CONTROLLED RELEASE METOPROLOL TARTRATE TABLET DEVELOPMENT AND EVALUATION

Thesis Submitted To The

BUNDELKHAND UNIVERSITY
JHANSI

BY

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M. Pharm. (Pharmaceutics)

IN FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY
(PHARMACEUTICS)

MARCH 2005

Dedicated

to

Daddy & Mummy

for their

constant unconditional

love . . . .

BUNDELKHAND UNIVERSITY
Jhansi – 284 128 (UP)

Certificate

This is to certify that the thesis entitled, **"Controlled Release Metoprolol Tartrate Tablet Development and Evaluation"** was carried out by ***Gayathri V. Patil,*** under the guidance of ***Prof. Sujata K. Dass***, in partial fulfillment of the requirements for the award of the degree of **DOCTOR OF PHILOSOPHY IN PHARMACEUTICS**, is forwarded to **Bundelkhand Univeristy, Jhansi.**

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This is forwarded to **Bundelkhand University Jhansi**, in partial fulfillment of the requirements for the award of **DOCTOR OF PHILOSOPHY IN PHARMACEUTICS.**

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I further declare that I have not submitted this dissertation previously for the award of any degree or diploma by me.

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ACKNOWLEDGEMENTS

*I express my deep sense of gratitude to my apt research guide **Prof. Sujata K. Dass**, to whom I sincerely owe this thesis.*

*My many thanks to **Dr. Kamalesh Oza**, Colorcon Asia Pvt. Ltd., Mumbai & **Dr. K. R. P. Shenoy**, GM, QA & Tech. Services of AstraZeneca, B'lore for free & generous supply HPMC and Metoprolol tartrate respectively, which enabled me to take up laboratory work. I acknowledge, **AICTE, New Delhi** Project F.No.1-51/CD/CA (CAO59)98-99 for the research support; initially. I am indebted to the Principal, KLES's COP, B'lore, **Prof. B. G. Desai** for permitting me to undertake following studies at the college: evaluation of marketed metoprolol tablets, FTIR spectra, chromatographic analysis.*

*I fail in words to express my emotional regards to the Ex-principal, KMK's COP, Mumbai, **Prof. J. K. Lalla**; honorable Vice Chancellor, Bundelkhand Univ., Jhansi, **Prof. Ramesh Chandra**, Chairman, KLE Society, Belgaum, **Shri. Prabhakar Kore**; & Principal, KLES's COP, Belgaum, **Prof. F. V. Manvi** for the constant support, care & concern.*

*I am thankful to the assistance of my students **Shruti** & **Rajeev**.*

*Feel blessed for the familial understanding & emotional cushioning of **Brownie**, **Siddu, Ashwani, Happy, Sach, Shashikant Sharma sir, Ajay Gupta, Namdeo sir, Sunil sir**.*

The achievement is not mine but of the family; standing by me.....

Gayathri V. Patil

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CHAPTER 8. RESULTS AND DISCUSSION

Research Envisaged...

INTRODUCTION

With the advent of capital investment and commercialised finance in production and distribution of Pharmaceutical Products and Services, the traditional ways of preparation/dispensing of medicine got a total transformation unlike any other modern industry, catering to the social needs and to the individual human being; maturing in multinational corporation.

It is through these capitalized channels, pharmaceutical products and services became accessible to common man – democratising this vital service. Capitalization of Pharma-industry contributed to strategic research and developmental process, producing "**quality therapeuticals**" in the process of its sustenance, survival and growth; in the tough competing marketing network.

The developed countries first related Trade Related Intellectual Property Rights (TRIPS) with the development of trade, investment and services during the General Agreement on Trade and Tariff (GATT) negotiations, which began in Uruguay in 1986. Now they want to carry logical conclusions on Patent Regulations.

RESEARCH ENVISAGED

1. India is a signatory to GATT Patent Law, effective from January 2005. Its implications on Pharma-industry are of paramount significance at both national and international level for India's proven standing capability of producing quality medicines at cheapest price in the world. Hence, it was thought to take a quick review of the Indian **PharmaTech Industry** and the international scenario in this transitional IPR regime – **FIRST OBJECTIVE**.

2. Hypertension is a aging phenomenon or life style disease or affliction Therefore, its was felt to undertake a short survey to study the various aspects of this disease – namely awareness in patient for this affliction, their attitude and approach for the therapy (both pharmacological and non – pharmacological) and compliance with drug therapy – **SECOND OBJECTIVE**.

3. Government of any nation is accountable and is expected to uphold the interest and well being of its people. The Indian Government is putting efforts and is of the opinion to impress the Medical community to go for prescription of Generic rather than branded drugs so that the patient can be benefited spending less on the medicines. Hence, it was thought to evaluate the available marketed products of Metoprolol Tartrate 50 mg Tablets as per the Official Specifications and estimate the cost projections for 1 year based on the drug regimen in each – **THIRD OBJECTIVE**.

4. Hydrophilic non-disintegrating controlled/extended drug delivery established a better drug delivery system for oral route over multiparticlulate beads/ micropheres, pellets etc., and has gained wider acceptance for it high-speed production and economic reasons. Therefore, it was thought to prepare and evaluate hydrophilic controlled release matrix system using hydrophilic polymers containing the active drug metoprolol tartrate and scale up to lab. pilot size (till *in vitro* dissolution stage) based on the experimental protocol using FDA's Guidance for Industry SUPAC-MR: Modified-Release Solid Oral Dosage Forms, Scale-Up and Post-approval Changes: Chemistry, Manufacturing, and Control; *in vitro* and *in vivo* Bioequivalence Documentation (Sept. 1997) – **FOURTH OBJECTIVE**.

Chapter 1

PharmTech Industry...

1.1. MARKET REVIEW

1.1.1. World PharmTech Market

The world pharmaceutical market is estimated to swell to 550 billion USD by 2005[1]. The year wise details of global pharma forecasts from 1996 are given in Table 1.1[2]. The world pharmaceutical market grew by ~0.92% in 1997, with an estimated sales reaching $ 294 billion from $ 292, to $ 505.8 billion in 2004, with an average annual global sales growth of ~7.16%[3]. Looking in the market trend *Dr. Joe Zammit* – Lucia, president of Cambridge Pharma Consultancy comments, *"The sustained growth of the world pharmaceutical market shows that consumers and health care professionals continue to appreciate the value of pharmaceuticals as a convenient, cost effective form of treatment".*

Table 1.1. World pharmaceutical market size.

Year	1996	1997	1998	1999	2000	2001	2002	2003	2004
Size (in USD billion)	292.0	294.8	304.2	338.0	373.0	406.9	438.0	469.4	505.8
Source: Global Pharma Forecasts[3].									

1.1.2. Leading Countries

The top ten worldwide markets represent approximately 79% of all unaudited and audited sales[4] is given in Table 1.2. The US remains the largest pharmaceutical market by far, growing 17% to $130.1 billion in sales in 1999, and representing 39% of the total worldwide market. Japan, the second largest market, recovered last year from three consecutive years of negative performance, growing 23% with sales of $53.5 billion. Within the top five European markets, Germany remains in the lead, achieving sales of $18.5 billion with 1% growth over 1998. The fastest growing Western European markets in 1999 were the UK, growing 8%, and Spain, with 6% growth over 1998. Brazil, the seventh largest audited world pharmaceutical market in

1998, dropped to eighth place last year, experiencing a 26% decline in growth due to economic conditions. China, ranked ninth for the third consecutive year, achieved $6.2 billion in 1999 sales and 12% year-over-year growth.

Table 1.2. Leading countries global pharmaceutical sales.

Rank	Country	1999 Sales*	% Global Sales	% Growth Year-on-Year*
1.	United States	130.1	39	17
2.	Japan	53.5	16	23
3.	Germany	18.5	5	1
4.	France	17.8	5	0
5.	Italy	11.3	3	3
6.	United Kingdom	11.0	3	8
7.	Spain	6.6	2	6
8.	Brazil	6.3	2	(-26)
9.	China	6.2	2	12
10.	Canada	5.5	2	11

Source: IMS HEALTH[4], (*Growth measured in USD Billion).

1.1.3. Domestic Market

The total annual domestic pharma sales is pegged at Rs. 18400 crores, according to retail audit figures for 12-month period ending June 2003[5], Table 1.3. The largest therapy segment are antibiotics and antibacterial systemics with a sale of 3137 crores but is showing degrowth by 2%. The hypotensive constitutes the eight largest segments under the study with the highest growth of 20.8%, while the anti-diabetic is second with 17.6%. The study shows that hypotensives, anti-diabetics and anti-asthmatics are registering good growth while antibiotics, the largest segment is

showing degrowth by 2%. A share of 54.73% of total annual sales comes from the top 10 therapy segments.

1.1.4. World Market Favorable To Generics

According to Glossary of Terms, **United States Food and Drug Administration** (US FDA)[7], a ***"generic"*** drug is the same as a brand name drug in dosage, safety, strength, how it is taken, quality, performance, and intended use. Before approving a generic drug product, FDA requires many rigorous tests and procedures to assure that the generic drug can be substituted for the brand name drug. The FDA bases evaluations of substitutability, or **"therapeutic equivalence"** (TE) of generic drugs on scientific evaluations. By law, a generic drug product must contain the identical amounts of the same active ingredient(s) as the brand name product. Drug products evaluated as TE can be expected to have equal effect and no difference when substituted for the brand name product.

Generic drugs have assumed a prominent role in the pharmaceutical industry. The modern generic industry only began in 1984 with the passage of the Drug Price Competition and Patent Term Restoration Act[8]. *"It is an established trend world over that the prices of generic drugs are much lower than the branded versions"* says *Mr. H. S. Sikka*, Senior President, Corporate Affairs, Nicholas Piramal India Ltd.[9], because they do not have to duplicate the cost of research and marketing conducted by the original manufacturer[10]. Generic medicines are considered as cheap bio-equivalent copies of molecules for which patents have expired[11]; typically introduced at 20 to 25% of the branded drugs price[8]. *Pankaj Patel*, Managing Director, Zydus Cadila: "*With rising healthcare cost, governments in the developed countries are coming out with regulations that increasingly favor generics. In France for instance, the government has started encouraging prescription of generics*[11]". It is estimated

that drugs worth US $ 31 is expected to face patent expiry in the years leading to 2010[12], Table 1.4.

Table 1.3. Domestic sales and trends of top 10 therapy segments.

Rank	Segment	Sales (in Crores)	Trends (in %)	Market Share
1.	Antibiotic & Anti bacterial	3137	- 2	17.05
2.	Vitamins	1079	+ 3.5	5.86
3.	Anti-inflammatory & Anti-rheumatologicals	1023	+ 2.6	5.56
4.	Cough & Cold	909.5	+1	4.94
5.	Antacids & Anti-flatulents	847.9	+ 5.9	4.61
6.	Antidiabetics	788	+ 17.6	4.29
7.	Cardiac	698.9	+ 7	3.8
8.	Hypotensive	650.16	+ 20.8	3.35
9.	Anti-anemics	477.98	- 2	2.6
10.	Anti-asthmatics	457.99	+ 11.8	2.49
	Total	10069.43		
Source: EPP New Bureau, Express Pharma Pulse, 2003[6].				

Taking a cue from UK's National Health Services (NHS), the Indian Government is looking at the option of asking the medical fraternity to prescribe generic drug, in order to bring down the prices of essential drugs[9]. However, generic companies allow middlemen and retailers to milk patients by quoting **Maximum Retail Price** (MRP) at par with branded names. A study initiated by the Chemicals and Fertilizers

Table 1. 4. Values of drugs going off-patents.

Values of drugs facing expiry till 2010	2003	2004	2005	2006	2007	2008	2009	2010
Values (in US $ billion)	6.6	3.8	7.0	2.8	4.0	2.0	3.2	1.6
Source: Iyer, Express Pharma Pulse[12].								

Ministry has revealed that the difference between the cost of production of a generic drug and its MRP is very wide and the margins are either given to the chemists or doctors who prescribe them.

Office of Planning, US FDA, in November 2003[13], released **White Paper** stating that generic drug prices in the US are lower than drug prices in Canada. Canadian branded and generic prices relative to U.S. generic prices for these seven drugs appear in the Fig. 1.1. Only one (metformin) sold for less in Canada either generically or as a brand name. Furthermore, metformin did not become available generically in the US until January 2002, so US generic prices have likely not fallen to the level they will eventually reach.

1.1.5. Reforms In Generic Marketing

Recent reforms by the US FDA to the procedures required for entry into the generic market and to the protections provided to patents of the innovator companies were put forth to restore and enhance balance to the playing field of pharmaceutical marketplace[15]. The new rules come in response to what many consider loopholes in the original **1984 Hatch-Waxman Legislation** for abbreviated generic approval. The reforms, labeled the Final Rule by the FDA, have two central accomplishments. The first is the elimination of the possibility of obtaining multiple 30-month stays against a

single **Abbreviated New Drug Application** (ANDA). And second are more – stringent requirements for patent listing in **Orange Book**. It will behoove those on both sides of the issue to pay close attention to the new regulations.

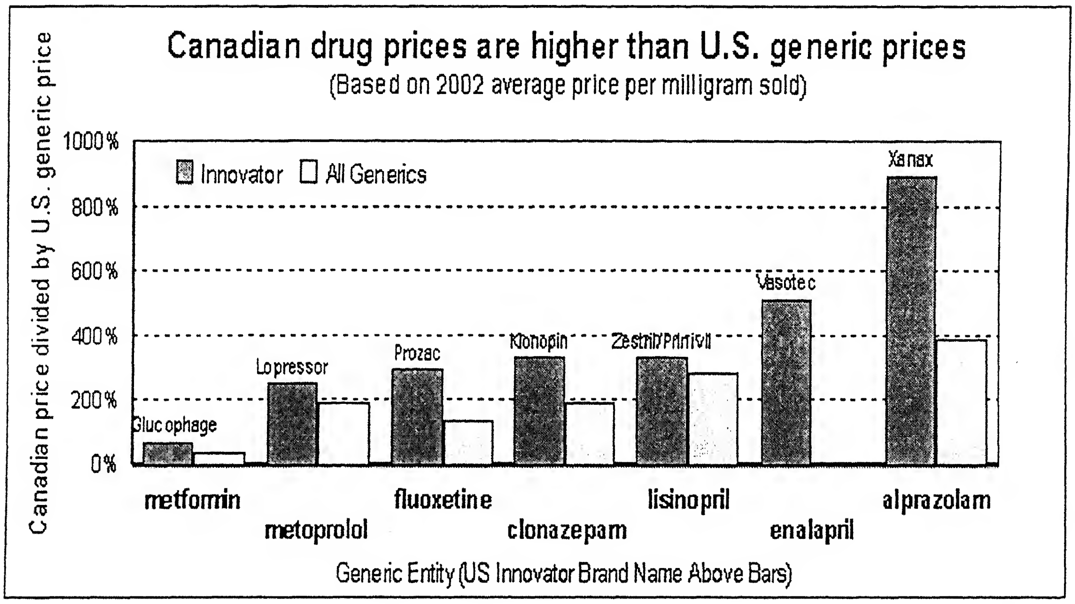

Fig. 1.1. Canadian drug prices are higher than US generic prices[13].

1.1.6. Origin of Patents and Development[16]

Developed countries first linked intellectual property rights with the development of trade, investment and services during the **General Agreement on Tariffs and Trade** (GATT) negotiations, which began in Uruguay in 1896. This international regime, given a final shape in **Trade Related Intellectual Property Rights** (TRIPS) had no caveats and no member country could withdraw form it. The only concession given to developing and **Least Developed Countries** (LDCs) was an initial discretion in implementing the provision, which were to be progressively eliminated.

However, the derailment of the **World Trade Organization's** (WTO) Seattle Ministerial Conference in 1999 by anti-globalization activists forced a rethink. The Doha Ministerial Conference in 2001 adopted the Doha Declaration in which

countries agreed to implement the TRIPS agreement in a manner supportive of the WTO member's right to take measures to protect "human, animal, plant life or health or of the environment at the levels it considers appropriate". India, along with Brazil and South Africa, played a crucial role in bringing together developing countries on the issue.

According to TRIPS, while developing countries (which includes India) had time until January 1, 2005, to enact domestic legislation to conform with the agreement, LDCs were given time until 2016.

1.1.7. Intellectual Property Rights

Thomas Jefferson[17], on intellectual property – "*If nature has made any one thing less susceptible than all others of exclusive property, it is the action of the thinking power called an idea, which an individual may exclusively possess as long as he keeps it to himself; but the moment it is divulged, it forces itself into the possession of everyone, and the receiver cannot dispossess himself of it. Its peculiar character, too, is that no one possesses the less, because every other possesses the whole of it. He, who receives an idea from me, receives instruction himself without lessening mine; as he who light his taper at mine, receives light without darkening me. That idea should freely spread from one to another over the globe, for the moral and mutual instruction of man, and improvement of his condition, seems to have been peculiarly and benevolently designed by nature, when she made them, life fire, expansible over all space, without lessening their density at any point, like the air in which we breath, move, and have our physical being, incapable of confinement or exclusive appropriation. Inventions then cannot, in nature, be a subject of property.*" But still, we continue to have **Intellectual Property Right** (IPR) Law it, with unlimited justifications and reasoning in the interest of development of Science and

Technology in the service of the mankind! The steps[18] involved in obtaining a patent is given in fig.1.2.

1.1.8. Indian Patent Act, Post GATT Scenario and Strategic Transnational Growth

Intellectual property has assumed a completely new dimension in India after the turmeric, neem and the basmati disputes[19]. The story of patents in India dates back to the first Indian Patent law - which was enacted in 1856 and modeled on the same lines as the British Patent Act of 1852. A proper institution and authority for the administration of patents, however, was not established until the appointment of the Controller of Industrial Patents and Designs by the Indian Patents and Designs until as late as 2000, when the Indian Designs Act of 1999 was enacted.

In 1959, the Government of India appointed the **Justice *Rajagopala – Ayyangar* Committee**[20] to suggest revisions to the Patent Law. In 1965, based on this report, a bill was introduced, but this bill lapsed in 1965 and again in 1966. This bill was re-introduced in 1967 and eventually passed as the **Indian Patent Act (IPA) of 1970**. The rules based on this act were passed in 1971 and the act along with the rules came into force in 1972. This legislation prevailed in the country undisturbed despite the passage of Super and Special 301 and threats from the US[19]. The conclusion of the Uruguay Round in 1994 paved the way for the change in this area of law. More importantly, India joined the WTO[21] and became obligated to comply with the TRIPS[22].

Today the market potential in India has attracted a new wave of investment by foreign multinationals and the talent generated in India is recognized across the world, making the need to merge with the rest of the world even more imminent, for which there need to develop a system were in the Indian companies and lawyers

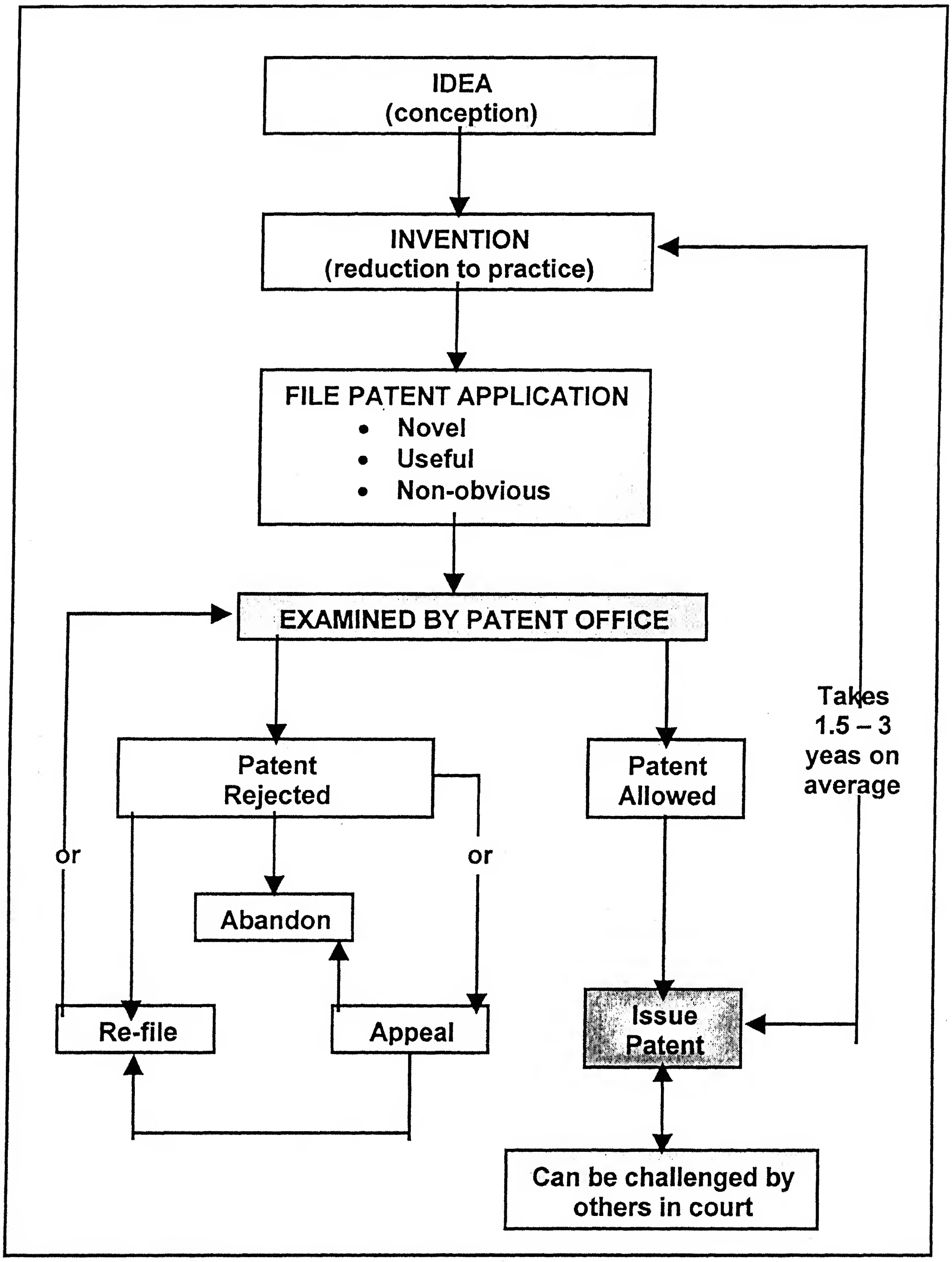

Fig. 1.2. Key steps involved in obtaining a patent.

meet their foreign counterparts in national and international forums. With lack of professional depth and efficiency will be the causalities, which will be detrimental to India on the long run[23].

Ganeshan[24] reports that around 650-patented drugs were introduced in the world market in the past 15 years (from 1983 to 1998) of which 72 were introduced into the Indian market under the existing dispensation between 1986 and 1988. In the last five years, i.e. 1994 to 1998 alone, 39 new drugs were introduced in the Indian market. There has generally been a gap of three to five years, if not more, between the introductions of a new patented drug in the world market and its subsequent introduction in the Indian market. It can therefore be surmised that the Indian market may, on ar. average, see 5 or 6 new patented drug introduction each year for the foreseeable future.

The Indian pharmaceutical industry has grown significantly after independence. The IPA 1970 was a landmark legislation, which in may way far exceeded the restrictions put on the patent system by other like minded counties such as Brazil, Argentina, Chile and China to enable local production and marketing of patented drugs at prices much lower than their counterparts in the patent-strong developed countries[25]. With only the process patent, various drugs, intermediates and chemicals were prepared by shorter synthetic routes than originally reported by the inventor, within a few months, by highly cost effective process[26]. Even though in terms of value terms, the Indian Pharma Industry has only 1% of the world market, in volume terms, Indian production of bulk drugs in 7-8% of global pharmaceutical out put in view of low prices commanded by the Indian Industries[25]. However, India become signatory to the GATT Patent Law effective from January 2005 which has taken Indian pharmaceutical industry at the crossroads. It is imperative that none can make drugs originally discovered and patented by others even by innovative new process without

paying royalties to the inventor. The increasing national and international competition, the collapse of geographical barriers, changing world markets, liberalization and globalization would radically influence the direction of the industry[26].

Shri. K. R. Narayanan, the 11th President of India (then an Member of Parliament) in his speech at the 3rd World Patent Convention[27] said, "*You know that the field (pharmaceutical and medicines), where the maximum pressure is being put on us. Almost all our countries are poor, our health standards are appalling and the great ideal of Health for All by 2000 A. D. – all these are before us. We will not be able to reach those targets. Not only that, we will not be able to provide even a minimum health standards for our people if markets for pharmaceuticals and medicines are cornered by the great transnational and not by our own developing, rapidly growing pharmaceutical industries. This is a human question, protecting the health of our people, and providing the human infrastructure for the development of our country....; now we cannot just afford to yield on these issues because as we know our own future, our own development, our own welfare depends on the application of this new knowledge of science and technology particularly to the economic processes. It is not only for industries but also for agriculture ...*". Addressing the Asian Symposium[28] on Healthcare Industry titled "Regulatory policies and growth constraints" the OPPI President *Mr. Ranjit Sahani* who is also the Vice-Chairman and Managing Director of Novartis Ltd., that the country had substantial growth potential in areas of contract research, custom synthesis and generics. He also said, "*the competition itself regulates the markets in terms of price stabilization as evinced by the recently introduced voluntary price cuts in insulin*".

The Indian pharmaceutical industry has stood to the times. Is known to produce cheapest quality medicines, approved by the worlds leading regulatory authorities, says Pankaj Patel, Managing Director of Zydus Cadila, India[11, 16] (Table 1.5). It is the

probably the only industry of the country that has not suffered from any recession[29]. Already, Indian Pharma Companies have rolled up their sleeves for the post GATT situation, have made massive investments and are streamlining their strategies for the transnational growth by one/ or more of the following approaches[1, 11]:

1. Continue thrust on Para III filings - driven by patent expiry).
2. Be aggressive on Para IV filings – patent challenge route.
3. Launch innovative specialty products - Drug Master Files (DMFs – for bulk drugs) and Abbreviated New Drug Applications (ANDA –for formulation.

Besides, most of the India pharma companies have been investing substantial time and efforts in cutting edge Research and Development in areas of New Chemical Entities (NCE), Novel Drug Delivery Systems (NDDS), process research and collaborative research[11].

The Indian pharma market is currently valued at $4 billion, which is just 1% of the global pharma market of $400 billion. Of the total global pharma market, 90% of the total market is with the US, Europe and Japan. It is estimated that after 2005, large numbers of many blockbuster-patented drugs are going to be off patent, whose market size is $40 billion. After 2010, the size of the off-patent drugs market is estimated around $80 billion. This will provide attractive opportunities to Indian companies to tap the international market for these products. Key players of the Indian pharma industry who are making substantial investments are Dr Reddy's, Ranbaxy, Wockhardt, Sun Pharma, Cipla, Zydus Cadila Pharmaceuticals, Torrent Pharmaceuticals, Lupin's, Aurobindo Pharma, Alembic Ltd., JB Chemicals & Pharmaceuticals Shasun Drugs and Chemicals, Ind Swift Laboratories[11].

1.1.9. Headlines, Comments and Quotes

Matters concerning to Patents, its impact on industry and people has created lot of news. The opinion and views, developments and moves at international and national level by people, pharma-industry and government is cited below as perceived by the researcher crucial that would govern the future course of action, in this area affecting every citizen in health care policy matters.

Table 1.5. Comparison of drug prices, Indian and International (in Indian rupees)[16]

Drugs, dosage & packaging details	India	Pakistan	Indonesia	United Kingdom	United States
Anti-infective					
Ciproflaxacin, 500 mg, 10 Tabs.	29.00	423.86	393.00	1.185.70	2,352.35
Norfloxacin, 400 mg, 10 Tabs.	20.70	168.71	130.63	304.78	1,843.66
Ofloxacin, 200 mg, 10 Tabs.	40.00	249.30	204.34	818.30	1,973.79
Cefpodoxime rosetin, 200 mg, 6 Tabs.	114.00	357.32	264.00	773.21	1,576.58
Anti-ulcerants					
Diclofenac Sodium, 50 mg, 10 Tabs.	3.50	84.71	59.75	60.96	674.77
Ranitidine, 150 mg, 10 Tabs.	6.02	74.09	178.35	247.16	863.59
Omeprazole, 30 mg, 10 caps.	22.50	578.00	290.75	870.91	2,047.50
Lansoprazole, 30 mg, 10 Caps.	39.00	684.90	226.15	708.08	1,909.64
Cardiovasculars					
Atenolol,	7.50	71.82	119.70	N.A.	753.94

50 mg, 10 tabs.					
Amlodipine Besylate, 5 mg, 10 Tabs.	7.80	200.34	78.42	338.28	660.21
Anti-viral/fungal					
Zidovudine, 100 mg, 10 caps.	77.00	313.47	331.65	996.16	895.90
Zidovudine, 300 mg, 10 Caps.	274.00	N. A.	N. A.	4,767.02	4,988.62
Anti-histamine					
Caterizine, 10 mg, 10 Caps.	6.00	35.71	57.50	262.19	927.29
Anti-anxioltics/psychotics					
Alpramazoo, 0.5 mg, 10 Tabs.	7.00	160.57	31.05	N.A.	446.81
Fluxetine, 20 mg, 10 Caps.	25.80	444.53	143.40	395.79	1,416.42
Anti-cancer					
Boposide, 100 mg, 10 Tabs.	190.00	554.69	242.90	1,217.43	6,210.30
Cholesterol reducer					
Atorvastatin 10 mg, 10 T-bs.	39.00	N.A.	565.95	537.74	1,102.92
Anti-asthamatic					
Salmeterol, 25 mcg	210	N.A.	782.65	1,628.25	N.A.
Urology					
Sildenafil Citrate, 50 mg, 4 Tabs.	48.00	N.A.	1,356.93,	1,614.89	1,744.93

Conversion rate of exchange considered: U.S. dollar – Rs. 45.50, Birtish pound – Rs. 83.51,Pakistani rupee – Rs. 0.84, Indonesian rupiah – Rs. 0.005.

Source for prices: U.S. prices – Red Book 2002; U.K. prices – U.K. MIMS Feb. 2004, Pakistan – Pharmaguide, June 2002-03, Inida – IDR November/December 2003.

1.1.9.a. International

- **Global Impact of Indian Patent Act**[30]

  "Seldom has India's Parliament considered anything of such global import. If Parliament can preserve India's ability to provide generic(s) ... it will make the difference between life and death for millions of people at home and abroad".

- **India failing to take full advantage of WTO regime**[16]

  "A double hit that will cut off the supply of affordable medicines and remove generic competition that drives down the cost of brand-names", Editorial, The New York Times, Jan 18, 2005. It further the ordinance was (i) heavily influenced by multinational and Indian drug-makers eager to sell patented medicines to India's huge middle class; and (ii) so tilted towards the pharmaceutical industry that it did not even take advantage of the rights countries enjoyed under WTO regime to protect public health.

- **Indian contribution in cutting HIV/AIDS therapy cost**[16]

  "Two thirds of the world's population will be systematically deprived of life-saving drugs as of January 1, 2005. Countries in Africa dependent on Indian generic products, the WHO and AIDS organizations worldwide have written to Indian Prime Minister asking him to reconsider ordinance". Indian generic companies brought down the prices of antiretroviral therapy for HIV/AIDS from $ 12,000 to $ 140 a year.

- **Gaps in Patent Protection**[31]

  "At present, there are certain structural weaknesses in the Indian regulatory framework with regard to the drug approval process. The country also suffers from inadequate supporting infrastructure in patents protections.....; if you want to

compete with China, you need to significantly improve your long-terms investments in infrastructure and never compromise on global quality standards", *Dr. W. A. Saseltine*, Chairman, Scientific Advisory Board, Matrix Labs at BioAsia 2005.

- **Cautious Compliance**[32]

  "The fact that an Ordinance has been passed by the UPS Government amending the Patents Bill to comply with the TRIPS mandate does not necessarily mean that it has to become law", K. P. P. Nair, Former Science Foundation Professor, Royal Society of Belgium.

- **America's Patent System**[33]

  "America's patent system has become sand rather than lubricant in the wheels of American progress", Adam Jafee & Josh Lerner.

- **Indian Pharma-Company Globally Competent**[34]

  "India's pharma companies have achieved worldwide acceptance for their competency.....; Indian pharma companies offer above-average management, achieving superior revenue growth while maintaining good margins in a high competitive segment", excerpts from the report prepared by Mehta Partners, a New York- based global healthcare investments firm.

1.1.9.b. Experts

- **The People Commission Report on America's Stand**[35]

  "Whatever be the international commitments or agreements signed by it, if any agreement conflicts with the interests of the American people, the American law will prevail; the American law will subdue that commitment" - excerpts from The

People Commission Report (PCR) that refers to US making clear that its own interests will prevail when there is clash of other interests, as cited.

- **Patent – a techno-legal document**[16]

  "Patent is a techo-legal document. It is an important piece of legislation and should be considered by either a joint committee or a standing committee of Parliament", A. D. Damodaran, Former Director, CSIR, Regional Research Laboratory, Thiruvanthapurum.

- **Who Rules The Rooster**[35]

  "It is important to remember that industry-advanced countries such as the U.S. and the European Union together hold 97% of all patents world-wide and multinational corporations account for 90% of all product and technology patents, and if they choose to hold the rest of the world to economic ransom and we unwittingly succumb the perils of this game by thoughtless haste, posterity will blame us for out foolhardiness" K. P. P. Nair puts a word of caution.

- **Sustaining Post-Doha Obligations**[36]

  "By rushing through the Third Patents Amendment without proper parliamentary scrutiny, India is short changing its post-Doha obligations to both its own and the world's poor.....; patents are not a gift for drug companies to exercise power without responsibility", R. Dhavan.

- **Crux of WTO**[37]

  "WTO helps developed countries by design and developing countries by default", Mr. Rahu Bajaj, as cited.

1.1.9.c. National

1.1.9.c.i. Pharma-industry

- **Product Patent Regime**[38]

"India embarks a new regime of product patent after a gap of 35 years. The infrastructure need for a new regime is created, but not yet tested. The Patent Office has yet to demonstrate its maturity and skill sets for dealing with the new regime. Its track record so far has been dismal. It's tow of the four decision on EMS for pharmaceutical products (Glivec, an anticancer drug and Cialis, an impotency drug) are embroiled in the High Courts of Delhi, Chennai and Mumbai" – Representative, Indian Pharmaceutical Alliance (IPA) Representative cautioned the Government on the need to "clearly define" terms such as patentability.

- **Mailbox**[39]

"One doesn't know what will happen when the mail-box is opened", Mr. Malvinder Mohan Singh, Ranbaxy President – Pharmaceuticals and Executive Director, expressing concern over 'Mail-box Provision'.

- **Patent Bill In Present Avatar – Chaotic**[40]

"This could lead to chaotic situation as several companies would be forced to withdraw their bands from the market and the innovator entity will be able to jack up prices, hurting patients", Mr. Habil Khorakiwala, sounding a note of caution on Patents Bill in present avatar before the parliament;

- **Drug Price Control**
    - *"We are against price control for these drugs as these are high-tech drugs and low volumes. Any type of control will hit availability as companies could stop manufacturing"*[41], *Mr. S. Reddy*, MD, Dr. Reddy's Lab. Ltd.
    - *"It has been amply proved that competition is the best controller of prices"*, cited from a recent study commissioned by IDMA[42].

- **Patenting and affordability**[43]

"If medicines have to remain affordable, countries will have to watch out that minor/trivial developments in a drug molecule do not get patented", Mr. D. G. Shah, Secretary General, Indian Pharmaceutical Association.

1.1.9.c.ii. Government

- **Drug Price Control**
    - *The new Patent Ordinance would not affect drug prices because the process of granting patent would take around two to four years and 3 per cent of the drugs would be patented and 97 per cent would remain outside its purview", Mr. Ashok Jha*, Secretary, Dept. of Industrial Policy and Promotions (DIPP), reacted over new patent norms and its impact on drug prices[44].
    - *"We will allow low margins up to a limit. The Government will take action if margins are very high", Mr. Ram Vilas Paswan*, Minister, Chemicals and Fertilizers in a meeting with representatives of the pharmaceutical industry[45].

- **Compulsory Licensing**[46]

  "Certain drugs, which are protected by patent, must be made available through the compulsory licence route", Mr. Ram Vials Paswan, Minister of Chemical and Fertilizer, addressing the Group of Ministers (GoM) set up to look into the amendments to the Patent (Amendment) Bill 2004.

- **Pre-Grant Objections**[47]

  "We did not want a situation where pre-grant cases can be dragged. The Law will take care of genuine concerns. Specific timelines have been put in place for grant patents has been reduced from a maximum period of 104 months to 52 months and the minimum period from 27 months to 5 months" Mr. Ashok Jha, Secretary, Dept. of Industrial Policy and Promotions (DIPP), reiterating Government keeping in mind the interest of the consume and the domestic industry.

- **Opposition for the Patent Amendment Bill**[16]

  "We hav told the government that we will oppose the ordinance as tis is not in the national interest. It will have serious implications for the pharmaceutical industry, agriculture and biodiversity. The government have to amend it drastically keeping in mind the national interest. This is bound to come up in the coming Budget session and Left parties will take up the issue clause by clause", D. Raja, Secretary, National Communist Party, India.

- **Profiting from life and death**

  "My idea of a better ordered world is one which medical discoveries would be free of patents and there would be no profiteering from life and death", Ms. Indira Gandhi in World Health Assembly, 1981 Geneva, as cited[48].

1.1.9.c.iii. People

- **Democratising Drug Availability To Save Life[49]**

  'The Ranitidine preparation costs Rs. 740 (in rupee value) in the U.S. and Rs. 196 in Pakistan and this may well happen here. The process of patent system has been replaced by the product patent system because the Government in Delhi has placed its international obligations under GATT above national considerations....; considering that we have 18 lakh children dying each year because of lack of medical treatment and 1.3 lakh pregnant women dying during delivery, we cannot make medicine beyond the reach of those who badly need them'. Mr. Kumaraswamy, Convernor, Swadesh Jagrana Manch, Karnataka, expressing implications of the Ordinance amending the Indian Patents Act issued on December 26 by the Union Government.

1.1.10. Patent Issues

Experts of international repute in the field of Law, Economics, and Social Sciences etc. have expressing their opinion, cautioned over the consequences and suggested tactful ways of pursuing the issue in the interest of people at large. The article by *Abbot et al*[50] suggests how the four vital issues need to be dealt at the concerned level.

I. To prevent **"evergreening of Patents"**, patents only for modifications to New Chemical Entity (NCE) and for modifications to these entities that are clinically demonstrated to be significant therapeutic improvement over any previously patented form of the medicine should be granted. Such demonstrations, though not required under US or European Patent Law, is permitted by TRIPS.

II. Indian Law should retain maximum flexibilities available in TRIPS Articles 30, and particularly Article 31 relating to compulsory licensing. India currently allows the grant of compulsory licenses, but the procedure is cumbersome and offers many opportunities for patent holders to delay or prevent the grant of such licences. This process must be streamlined. In addition, the Ordinance imposes unnecessary hurdle on many developing countries without their own manufacturing capacity who might want to buy low-cost drugs from India as permitted under the Waiver to Article 31(f) and (h) of TRIPS adopted on August 30, 2003 by the WTO General Council. The Ordinance requires them to grant a **compulsory** patent licence even if the drug is not patented there. This hurdle is unnecessary, benefits no one, and is not required by the Waiver, of which India was, in fact, a champion! India's generic producers, who could produce for export, need as much breathing space as can legally provided without violating TRIPS so that they continue their successful supply of low-cost products to Indian and World markets.

III. IPA of 1970 included a so-called "pre-grant opposition" right to third parties seeking to challenge a patent application before the patent was granted. The Ordinance apparently changes this from a right to a discretionary act by the Controller General of Patents who decides whether a challenge should be allowed. Since, the TRIPS Agreement as well as patent laws in a number of developed countries permit the use of pre-grant opposition, it is important for India to allow them. This is particularly important with respect to the Mailbox application because, without effective pre-grant opposition, generic producers may need to challenge thousands of improvidently granted patents in the courts, placing them at a significant disadvantage compared to the better financed foreign multinationals.

IV. Indian government should consider whether India would benefit form a global exhaustion regime – i.e., from allowing medicines that have been lawfully placed on the market with the consent of patent holder in another country to be imported into India. The US Congress is considering this as a strategy to lower the price of medicines. Finally, India should join with other like-minded developing countries in the ongoing Doha Round of multilateral trade negotiations in pressing for further liberalisation of Article 30 and 31 of TRIPS to enable developing countries to meet public health concerns in the manner they deem best. Countries should have the freedom to apply social cost-benefit calculus relevant to their circumstances in a transparent and predictable manner in determining whether to grant a patent and, if so, on what terms.

1.1.11. Survival Strategies of Indian Pharmaceutical Companies[25]

Post 2005, survival will largely be governed by fundamental strengths in developing NCEs. The average cost of developing an NCE is 350 million USD with a time span of 10-12 years and a success rate of 1 in 10,000. Considering the cost and the uncertainty of new drug discovery, an alternative strategy would possibly be to produce and competitively exploit technologically advanced products in new areas with demonstrable benefits, preferred by clinicians and patients over the less expensive generic version of original branded products[8]. This strategy would include the development of NDDS, an area hitherto neglected by the industry due to lack of product patents.

1.1.12. Indian Market of Cardiovascular Drugs

From the study[51] over a period of two years from April 2000 to April 2002 it is concluded that the drugs for cardiovascular diseases account for Rs. 591.87 crore, or ~ 3.81% of the total pharma sale of Rs. 15,533.84 crore per year in 2001. The top

sellers considered in this category amount to a total to Rs. 417.17 crore, i e, ~ 70% of the total sales of all cardiovascular products. The prices of cardiovascular drugs show an overall rise of nearly 5% over April 2000.

1.2. CONTROLLED DRUG DELIVERY SYSTEM

A separate industry has arisen that focuses on the improvement of drug delivery systems. Since R. P. Scherer & K. V. Pharmaceuticals were founded in the pre-World War II era, more than 100 companies have become actively involved in developing (ug delivery systems[8], and the industry is growing at a considerable pace. In 2002, revenues of pharma products, which utilized advanced drug delivery technology reached US $ 38 billion growth and will continue to steady average growth rate of 28% over next 5 years, reports Mindbranch, a market research group[52]. It is expected that by 2007, drug delivery will account for 39% of all pharmaceutical sales. The fast growth of this industry sector can be attributed to the following major developments

1. The need for effective delivery of new, revolutionary biopharmaceuticals.
2. Upcoming patent expirations driving pharma companies to reformulate their products.
3. New technologies can minimize side effects and lead to better compliance.

The worldwide market growth of controlled drug delivery systems[24] is shown in Table 1.6.

Table 1.6. Worldwide market growth in novel drug delivery segments (in US $ billions).

Technology	**2000**	**2005**	**Growth (in %)**
Controlled release	14.2	26.3	85
Pulmonary, inhalation	11.7	22.6	93

Transnasal delivery	8.2	16.0	95
Transmucosal	2.4	6.5	171
Transdermal delivery	6.7	12.7	90
Injectable/implantable	3.8	7.2	89
Needle-less injection	0.4	1	150
Rectal	0.5	1.2	140
Liposomal	1.2	3.3	175
Cell/gene therapy	0	5	0
Miscellaneous	1.5	2.5	67
Total	50.6	104.3	106
Ref.: H. Sen., Ph.D. thesis, 2003[26].			

The growing global market in new technologies[52] could be of the following types of drug delivery.

1. Polymers
2. Monoclonal Antibodies
3. Liposomes
4. Oral (controlled release) Delivery
5. Pulmonary Delivery
6. Injectable Delivery
7. Transdermal Delivery
8. Transmucosal Delivery
9. Implant Technology

The US demand for the oral drug delivery systems will expand 7.8% per year to $ 36.5 billion in 2007, according to a press release by the Cleveland-based industrial

market research firm, reports Mumbai's EPP News Bureau[5]. Details are given in Table 1.7.

Table 1.7. Drug delivery systems demand (US $ bn).

Route of Administration	1997	2002	2007	02/97*	07/02*
Oral	12.1	25.1	36.5	15.7	7.8
Parenteral	110.2	18.6	30.7	12.8	10.6
Inhalation	5.4	8.6	12.1	9.8	7.1
Transdermal & implantable	0.9	1.5	3.0	10.4	14.2
% Annual Growth. Ref.: EPP News Bureau, Mumbai[5].					

With the availability of new polymers and better understanding of how to circumvent first pass metabolism, drug delivery companies in developed countries, apply their technologies across a range of clinical segments. The challenges in drug delivery will be multiplied for delivering biotechnology based products, which due to their poor solubility, bioavailability, stability and extensive first pass have conventionally been delivered by the invasive injectable route, by non-invasive routes[26].

1.2.1. Advantages of Controlled Drug Delivery Systems

The sources of value in reformulation include extending patent life, patient convenience/ compliance improvement, improved therapeutic efficacy, reduced manufacturing costs, and market share expansion[8].

1.2.1.a. Value Of Patent Extension

Because patents guarantee market exclusivity and artificially high premiums, patent expiration translates into rapidly declining sales for brand-name pharmaceuticals[8]. In

US, generic versions of drugs are typically introduced at 20-25% of the branded drugs' prices. The branded drug's, market erodes rapidly and loses 60-80% of the total days of therapy within 6 months[8] - the influence of managed care and mandatory substitution laws[26]. A typical example is that for Diltiazem[8,26]. This drug was discovered by Hoechst Marion Roussel and patent on its product, Cardizem, expired in 1988. A drug delivery company, Mylan, reformulated it as Cardizem CD - a once-daily version of the drug, in 1992. In spite of the launch of a generic version of the conventional drug in 1993, the company retained 86% of sale of diltiazem after patent expiration only due to the CD version, details are shown in Fig.1.3.

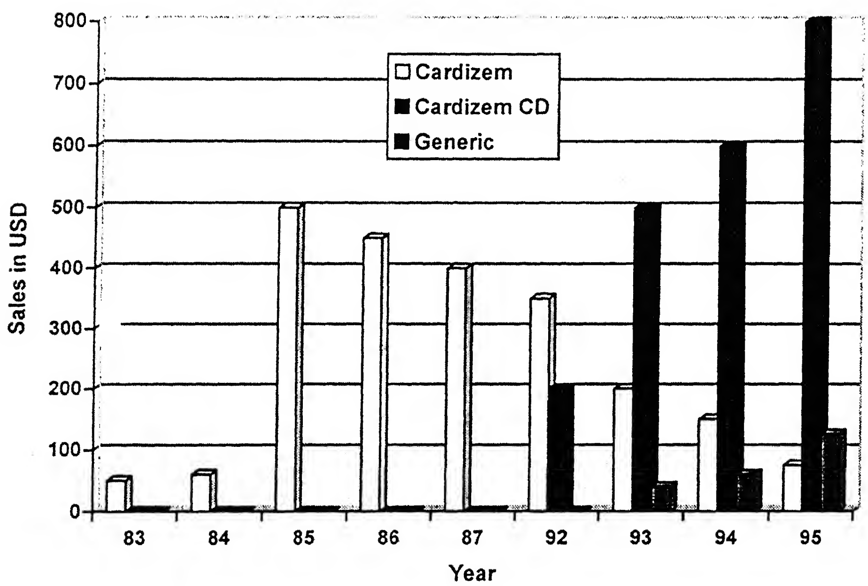

Fig. 1.3. Life cycle extension of Diltiazem, by developing a controlled delivery system thereof[8, 26].

1.2.1.b. Value Of Compliance Improvement

One of the most significant impediments to keeping patients healthy and curing disease is noncompliance with prescribed medication regimens. Regardless of any therapy's potential benefits, adherence to the prescribed regimen – the correct timings, dosage, method of delivery, physical status - determines the drug's ultimate success. Many factors influence patient compliance, including the nature of the

disease and disease symptoms, cognitive or functional ability, and financial resources. Some important factors influencing compliance, the frequency and mode of administration and the extent of drug-related side effects, can be modified through drug reformulation[25]. A survey study on relating to this aspect is shown in the later chapter.

1.2.1.c. Frequency and Mode of Administration

Clinicians have learned that to achieve high patient compliance, in the absence of serious noncompliance penalties, drug regimens must be convenient and uncomplicated. Inconvenient (injectables) or complex (many dosage per day) regimens lead to poor compliance[8]. The oral formulation is the most preferred mode of administration as it is the easiest form for patients to tolerate. Fig. 1.4 shows that 76% of the market value for top selling 100 conventional drug products in US comes from the oral systems; similarly, as shown in Fig. 1.5. among the drug delivery systems, oral drug delivery systems contribute a major portion of the pie[26].

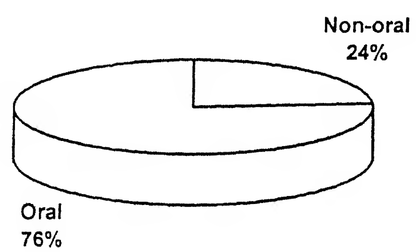

Fig. 1.4. Top 100 Drugs - U.S. Market Value.

In terms of the frequency of administration, less is more. Drugs that must be taken only once per day are ideal, because they gain the highest compliance. Compliance has been shown to drop off sharply for drugs that have to be taken more than three

times per day, thus drugs with more frequent dosing schedules are generally considered unacceptable for therapies that must be taken chronically[26].

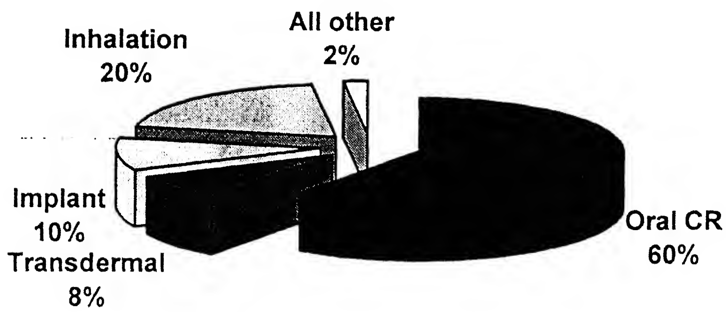

Fig. 1.5. Types of Drug Delivery Systems

A sustained release oral reformulation that allows for once per day dosing is the preferred form of drug delivery. Aerosol formulations have not been as convenient as oral because they have often required frequent (three or more times per day) dosing. In addition, the effectiveness of aerosol formulations has been hampered by the inconsistency of inhalers, which results in inadequate or varying levels of drug absorption. Nasal delivery has also lacked consistency in dosage absorbed due to backflow of drug after administration and variations in nasal architecture and volume of mucus between patients. Transdermal systems although usually providing dosing from 3-7 days, are perceived by patients as less attractive because patches can result in skin irritation and may not adhere to the skin efficiently. Depot injections offer significant improvement over frequent injections or intravenous infusions[8].

The most successful drug delivery formulations have been, as would be expected, oral sustained release formulations. Currently, Bayer AG's Adalat CC product for

hypertension leads the oral sustained release market. Reformulated in 1993 from a 3-4/day to 1/day, Adalat CC has climbed the sales of $ 1.1 billion worldwide in 1997. Another highly successful reformulation has been TAP Pharmaceuticals' Lupron Depot for prostate cancer and endometriosis. Reformulated from a daily injection in 1989 to a once per month injection, Lupron Depot has climbed to worldwide sales of $ 990 million in 1997[8,26].

1.2.1.d. Therapeutic efficacy[8]

Drug delivery technologies can improve medical outcomes not only by affecting compliance but also by improving therapeutic efficacy. Improvement in bioavailability may help drugs work more effectively, as can technologies that allow the release of the drug at specific times. For example, Covera HS, an Alza reformulation of hypertensive drug initially launched by Searle in 1996, is designed to deliver peak concentrations when blood pressure and heart rate are at their highest.

1.2.1.e. Extent and nature of side effects[8]

Side effects are common with many drugs and eliminating them can significantly increase the value of therapy. Side effects may be caused by the action of the drugs' active ingredient and therefore are unavoidable. However, drug delivery technologies can reduce or eliminate side effects.

1.2.1.f. Value of Reduced Manufacturing Costs[8]

One method of increasing profitability on a drug is decreasing manufacturing costs. Often orally formulated drugs with poor bioavailability must be administered in high doses, because only a small percentage of the active ingredients is absorbed by the body. Drug reformulations that improve the bioavailability of the drug require less active ingredient to produce an equivalent therapeutic effect, thereby reducing

manufacturing costs. Maximizing the bioavailability of these types of agents will be rewarded in the market.

1.2.1.g. Selection of drug candidates[8,26]

One of the most critical components of a drug or drug delivery company's strategy is the choice of which compounds to reformulate. This process should include the following explicit steps: developing a starting list of drug candidates, examining the delivery technology, assessing the therapeutic or administrative unmet needs, performing a competitive screen, and sizing the market.

Because there is considerable value in extending the patent life of a compound, drug companies often focus on their blockbuster drugs that are coming off patent for developing novel drug delivery systems. The pharmaceutical industry's "graveyard" is another source of drug candidates that have clinical potential but have failed in clinical trials due to side effects or administrative problems. There may be even more value in resurrecting these drugs that have consumed costly drug approval and / or market acceptance without reformulation.

The sophistication of controlled drug delivery technologies is advancing rapidly and companies' success rates are growing. As a result, in the longer term, pharmaceutical companies will proactively elect to reformulate drugs well before they reach their patent maturities. As a recent example, Pfizer announced that is was teaming with R. P. Scherer to reformulate a faster-acting form of its blockbuster Viagra less than 4 weeks after it launched the drug. In fact, as drug delivery matures as a science, pharmaceutical companies will involve the technologies in their initial formulations.

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Chapter 2

Case Study of 250 Hypertensive Patients...

2.1. INTRODUCTION

As the average human life expectancy has increased, so has the impact of ageing and age-related diseases on our society. Hypertension is one of the aging afflictions. It is in itself not a disease but is a condition of consistently raised blood pressure (BP) above normal. Essential hypertension, known as "the silent killer" does not cause symptoms for many years until a vital organ is damaged[1]. It is one of the major risk factors for coronary heart disease and the most important risk factor for cerebrovascular diseases[2], that are the leading causes of morbidity and mortality[3]. Multifactorial in origin[4], essential hypertension cannot be cured but can now be controlled[5,6] effectively, thanks to the progress made in biomedical and pharmaceutical sciences.

2.1.1. Definition of Hypertension

Blood pressure (BP) in its simplest terms is the force of the heart pumping action working against the resistance provided by the blood vessels. The purpose of the "blood pressure system" is to maintain blood flow to all of the tissues of the body at rest or during movements. To compensate for gravity, changing levels of activity, and other perturbations to the system, several interactive subsystems work to maintain tissue perfusion each with its own response time[7]. The Joint National Committee and World Health Organization (WHO)[2] adopted BP values as given in Table 2.1.

2.1.2. Management of Hypertension

Hypertension can now be controlled[6] and no longer is high BP a potential death knell for people in the prime of life. This progress is directly attributable to the biomedical research. By developing drugs that can control hypertension medical sciences has systematically reduced the deadly

Table 2.1. Categories of a person's blood pressure.

Category	Systolic BP (mm Hg)	Diastolic BP (mm Hg)
Normal BP	Below 130	Below 85
High normal BP	130-139	85-89
Stage 1 (Mild) hypertension	140-159	90-99
Stage 2 (Moderate) hypertension	160-179	100-109
Stage 3 (Severe) hypertension	180-209	110-119
Stage 4 (Very severe) hypertension	210 or higher	120 or higher
The Joint National Committee and World Health Organization[2].		

consequences of hypertension; leading to longer, healthier and more productive lives.

Hypertension therapy aims to prevent complications that arise due to elevated BP with or without drugs depending on the condition and response of the patient towards therapy. Controlled clinical trials[8] have demonstrated that by use of medicine, BP can be brought in control; which has also decreased both morbidity and mortality due to cardiovascular disease. The other non-pharmacological approach[9] in the management of hypertension is through (a) weight control[10-12], (b) sodium restriction[13-16], (c) fat content[17], (d) alcohol restriction[18-20], (e) physical exercise[21,22] (f) relaxation therapies for stress reduction[23-25] and (g) potassium therapy[26,27].

It is desirable to attempt the non-pharmacological means to control BP in patients with mild hypertension[28,29] and also in patients receiving drug therapy so as to reduce the BP; as per the recommendations of World Health Organization for the

concomitant non-pharmacological intervention[29]. *Sainani*[30] argues that every patient of hypertension from the stage of pre-hypertension to stage II (moderate) hypertension should follow non-drug therapy. If non-drug therapy is strictly adhered, one can even prevent cases of pre-hypertension from progressing to hypertension stage and can reduce or stop the medications in stage I (mild) hypertension. In support, *Oats*[9] explains that if by minor alterations of normal activity or diet, the BP can be controlled or reduced to a satisfactory level, the complications of drug therapy can be avoided. Besides this, it allows the patient to participate actively in the management of his or her disease; giving an appreciating patient compliance.

Despite the availability of many newer antihypertensive agents, hypertensive patients remain at higher risks of premature death than the general population. This persistence of morbidity and mortality may be accounted for by the frequent failure to achieve adequate blood pressure reduction despite an extensive array of available antihypertensive agents. Such considerations have led to reassessment of the potential role of fixed-dose combination agents in the antihypertensive armamenta,.um. The rationale for combination therapy relates to the concept that antihypertensive efficacy may be enhanced when 2 classes of agents are combined. In addition, combination therapy enhances tolerability – 1 drug of a fixed combination can antagonize some of the adverse effects of the second drug. Fixed-dose combination therapy simplifies the treatment regimen, preventing treatment failures that might result from missed doses. An additional novel concept is the possibility of enhancing secondary effects on target organs, including regressing left ventricular hypertension and retarding progression of renal disease, by combination therapy over and above the effects expected from the fall in arterial pressure alone[31].

2.1.3. Epidemiology of Hypertension

Epidemiological studies show a steady increasing trend in hypertension prevalence over the last 40 years, more in urban than in the rural areas, converse to findings reported from developed countries where there is a significant decrease in its prevalence[32,33]. It is estimated that 15-25% of the adult population of most countries have elevated BP[34,35]. In India, hypertension is emerging as a major health problem[36], caused 2.3 million deaths in 1990 and is projected to double by the year 2020[37]. Hypertension is poorly controlled[38] and patient compliance is a big challenge in its treatment. Although approximately two thirds of these "hypertensive" have only mild hypertension, they have increased risk of cardiovascular disease[39,40]. The consequences of untreated hypertension are expressed as increased incidence of tissue and organ pathology involving brain, heart, kidneys, and blood vessels[39,41], Table 2.2. Worldwide prevalence estimates for hypertension may be as much as 1 billion individuals, and approximately 7.1 million deaths per year may be attributable to hypertension[42].

2.2. OBJECTIVE

The objective of the present study was to survey patient's personal attitude and approach towards one's own hypertensive condition in this region of country, through a questionnaire. Jhansi city has a population of 1088056.2, and ranks 94th in the country[43]. The literacy rate of urban population is 78.56 and 54.56% in males and females respectively, excluding 0-6 years age group[44].

2.3. METHOD

A questionnaire (Appendix I) was filled by the authors over an interview with the patient at various places like clinics, medical stores and hospitals, over a period of about 3 months from February-April 2004, to cover the target of 250 cases.

Table 2.2. Pathological risks of uncontrolled hypertension.

Target Organ	Clinical Manifestation
Brain	Strokes (cerebral vascular accidents), Transient cerebral ischemia
Heart	Acute myocardial infarction, Sudden coronary death, Accelerated ischemic heart disease, (angina, arrhythmias)
Kidney	Renal failure, Renal functional impairment
Blood vessels	Aortic aneurysm (fusiform, sacular, sissecting), Atherothrombotic obstruction and stenosis, Ocular fundi damage (spasm to papilledema), Peripheral vascular disease and claudication.
Ref. Timmermans and Smith, 1996[45].	

2.4. RESULTS AND DISCUSSION

2.4.1. Visit to Physician

In 250 cases studied, there were 174 males and 76 females (1:2.3) who visited the Physician for diagnosis/treatment. Less number of females could be indicative of (i) high tolerance level ir /laid back attitude or may be ignorance on part of the woman, or (ii) the prevalence could be actually less (which needs to be established by undertaking equal number of study cases in both sexes). Within females, the age group between 35-40 recorded the highest (23.68%) visit rates to the Physician; almost 3 times more while in men in the same age group it was only 7.47%. Visit to Physician in female population rose steadily until the age of 45 years in comparison to males, but later it declined. Details are given in Table 2.3 and Fig. 2.1. As these figures indicate that the woman develop high BP at early age. This needs substantiatio with large field studies. 8 males and 2 females were recorded to have high BP below the age of 30 years. All these patients were suffering from other diseases too besides being hypertensive, Table 2.4.

Table 2.3. Patients in different age groups clinically diagnosed for high blood pressure.

Age	Males (Number)	Males (%)	Females (Number)	Females (%)
25-30	8	4.60	2	2.63
30-35	5	2.87	4	5.26
35-40	13	7.47	18	23.68
40-45	31	17.82	13	17.11
45-50	33	18.97	14	18.42
50-55	34	19.54	10	13.16
55-60	24	13.79	6	7.89
60-65	12	6.90	2	2.63
65-70	12	6.90	4	5.26
70-75	2	1.15	2	2.63
75-80	-	-	1	1.32
Total	174	100.01	76	99.99

Table 2.4. Various diseases found in hypertensive patients below the 30 years.

Age (in years)	Clinical Condition	Blood Pressure
	MALES	
25	Burger's Disease	150/90
28	Status Epilepticus	160/96
28	Chronic retention of urine	140/90
28	Congestive Heart Failure, Diabetes	200/120
28	Etiology is not detected	160/100
29	Illeoceacal Hypertrophy, Uriteric stone	140/100
30	Tuberculosis	150/95
	FEMALES	
25	Pregnancy	125/90
28	Polio, Filariasis, morbid obesity, asthama	200/130

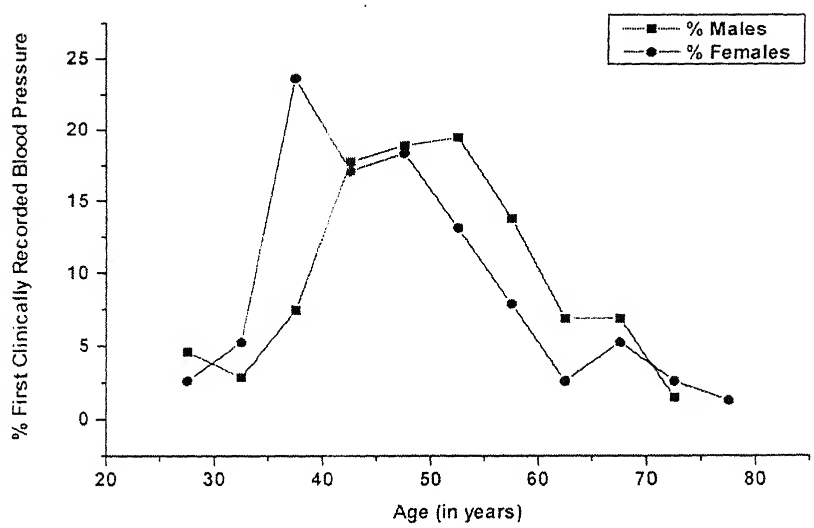

Fig. 2.1. % Frequency of high blood pressure with respect to age in males and females.

2.4.2. Patients Response Towards Their Own Hypertensive State

The patient's instant reactions for his or her own high BP were varied. 63.2% patients could not believe that they can have high BP (97 males and 61 females), while 24.4% patients (53 males and 8 females) had a feeling that they could have high BP while the rest of the 12.4% patients (24 males and 7 females) expressed that it did not make any difference to them whether they had high BP or not. In this group (of not to bother attitude), the BP ranged 140/90 to 210/130 and interestingly did not come in their routine day-to-day activities and performance; could either be because the patient did not care, or threshold of perception to discomfort was high or may be other problems took over the sensation over the persistent discomfort of their body. The study did not get further queries and details. Values are given in Table 2.5 and Fig. 2.2.

Table 2.5. Instant reaction to ones own high BP in hypertensive patients.

Type of reaction	Males	Females	Total
Could not believe	97 (55.75)	61 (80.26)	158 (63.2)
Was expected	53 (30.46)	8 (10.53)	61 (24.4)
Makes no difference	24 (13.79)	7 (9.21)	31 (12.4)
Total	174 (110.00)	76 (100.00)	250 (100.00)
Values in the parenthesis are values expressed in percentage.			

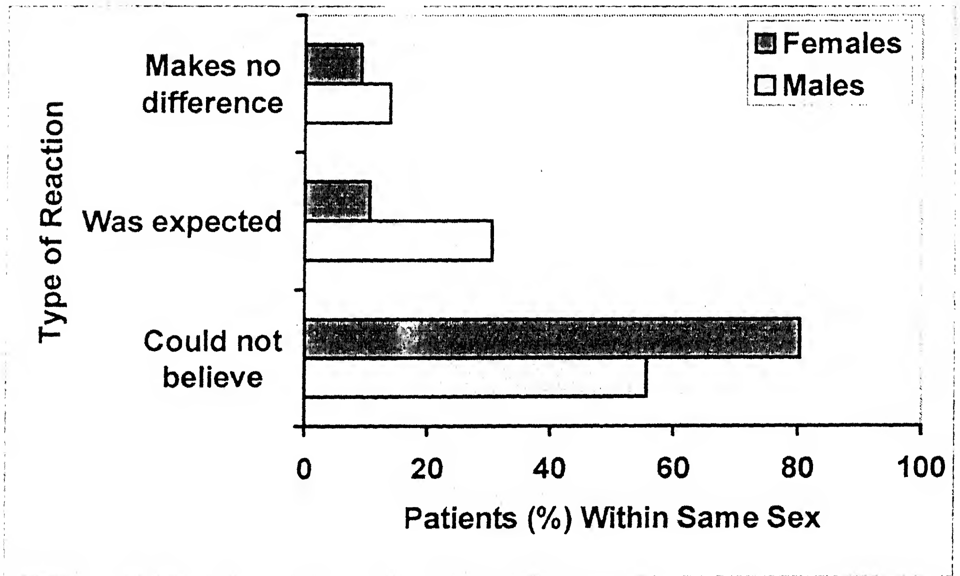

Fig.2.2. Type of reaction to ones own high BP state.

2.4.3. Control Of High Blood Pressure

On an average, 38.8% patients took 1 month, 28.8% patients took 3 months and 15.2% patients took 6 months time to bring down their BP to physicians anticipated level while in the remaining (17.2%) patients BP could not be brought in control well beyond 6 months period, Table 2.6. and Fig. 2.3.

Table 2.6. Time taken by patients to bring the high BP to the physician's desired level.

Time	Males	Females	Total
1 month	76 (43.68)	21 (27.63)	97 (38.8)
3 months	56 (32.18)	16 (21.05)	72 (28.8)
6 months	19 (10.92)	19 (25.0)	38 (15.2)
More than 6 months	23 (13.22)	20 (26.32)	43 (17.2)
Total	174 (100.0)	76 (100.0)	250 (100.0)
Values in the parenthesis are values expressed in percentage.			

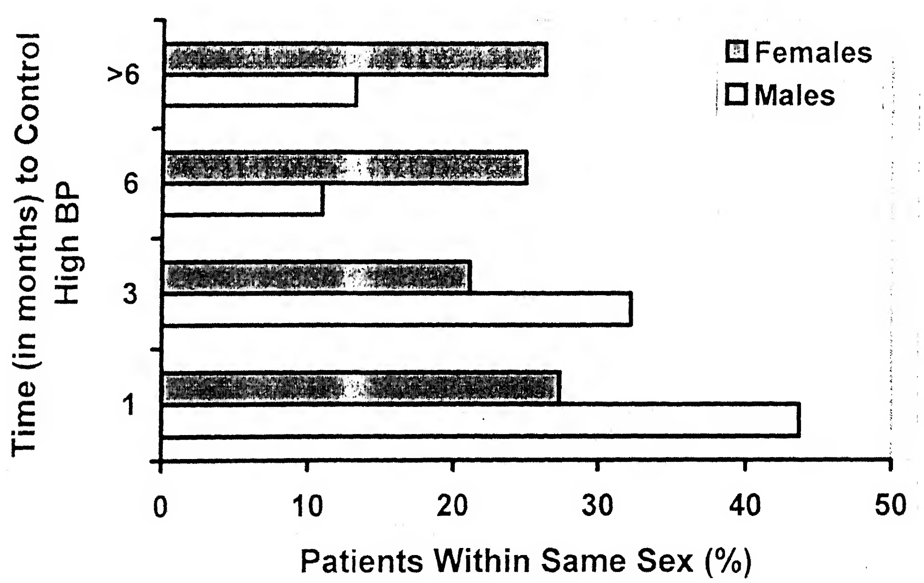

Fig. 2.3. Time taken by patients to bring the elevated BP to desired controlled level.

2.4.4. Complimenting Non-Pharmacologic Approach To Hypertension Management

2.4.4.i. Diet Control

It's reported that type of food has relationship with blood pressure[38]. Indians diet is mostly vegetarian. If non-vegetarian, then it is generally consumed 2-3 times a week. It was found that more females were towards vegetarian diet - 46 in comparison to 62 males. 33 males and 22 females were non-vegetarian; 33 males and 8 females were eggetarian. The calculated results in percentage are plotted in Fig. 2.4.

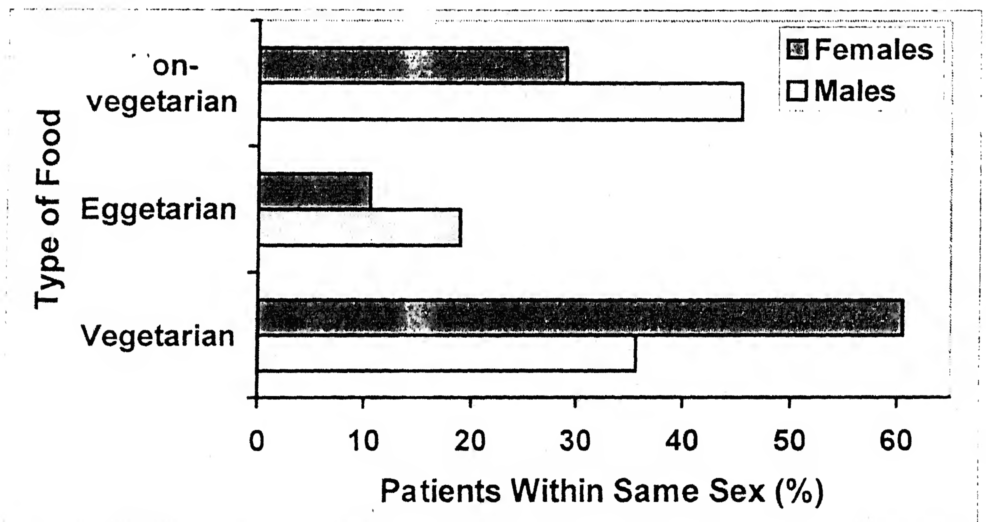

Fig. 2.4. Type of diet taken amongst hypertensive men and women.

The reason why woman scored high in vegetarian diet could be ascribed to their being (i) more religious and (ii) less occasion to interact with people and eat out. Woman are generally at home and those who are working also like to rush back to home from work place because Indian woman be it daughter, wife or mother is expected to deliver more services and monitor the home front compared to their counter part. There was no direct co-relation between food habits and elevated BP. From the study we found that ~81% females and ~77% males took care of their salt intake, ~41% females and ~31% males even controlled their fat intake, Fig. 2.5.

2.4.4.ii. Smoking And Drinking

It was interesting to note that there were two women were in the habit of smoking against the indian social taboo for a woman to smoke and drink (further enquiry revealed that these were tribal women). These ladies had begun to reduce their number of bidis (hand made cigarette), once they were counseled for its bad effects on their health. Amongst men ~24% were smokers, but once they were advised not to, they admitted to control. Those who were in habit of drinking also kept a watch on their beverage consumption, Fig. 2.5.

2.4.4.iii. Mind And Body Control Activities

The lifestyle, work, mental state of mind, attitude towards life etc. all has been suggested to contribute to elevate BP[23]. Walking is generally suggested along with other relaxation therapies[25,9]. In the survey group, the ratio of both males and females indulged who in walking was 41.1% (±0.3). Women were more inclined (48.7%) in religious and spiritual activities. However, double (14.4%) of the men population opted to reading when compared to women (7.9%). Details are given in Table 2.7 and Fig. 2.6.

2.4.5. Compliance To Drug Therapy

Despite the availability of a wide range of drugs that are effective at lowering blood pressure, survey[46-48] continue to reveal that those people treated for hypertension are often not controlled satisfactorily and many people discontinue their treatment. As mentioned earlier, patient compliance is a major hurdle in long-term continual therapy[38,49].

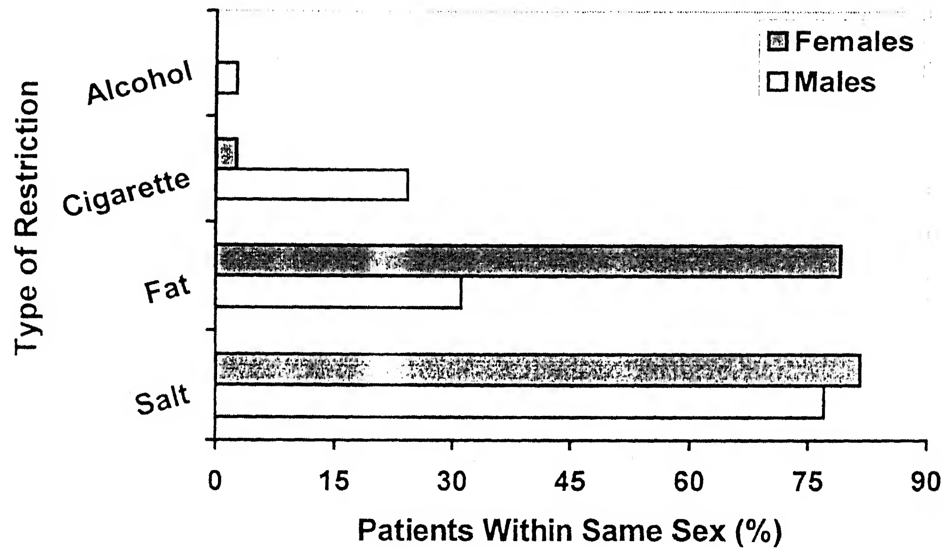

Fig. 2.5. Type of self-restriction.

Table 2.7. Supportive aesthetic approach practice by hypertensive patients.

Type	Males	Females	Total
Reading	25 (14.4)	6 (7.9)	31 (12.4)
Religion & Spiritual	54 (24.1)	37 (48.7)	79 (31.6)
Walking	42 (41.4)	2 (40.8)	103 (41.2)
Other physical activities	22 (2.3)	9 (11.9)	13 (5.2)
Values in the parenthesis are values expressed in percentage.			

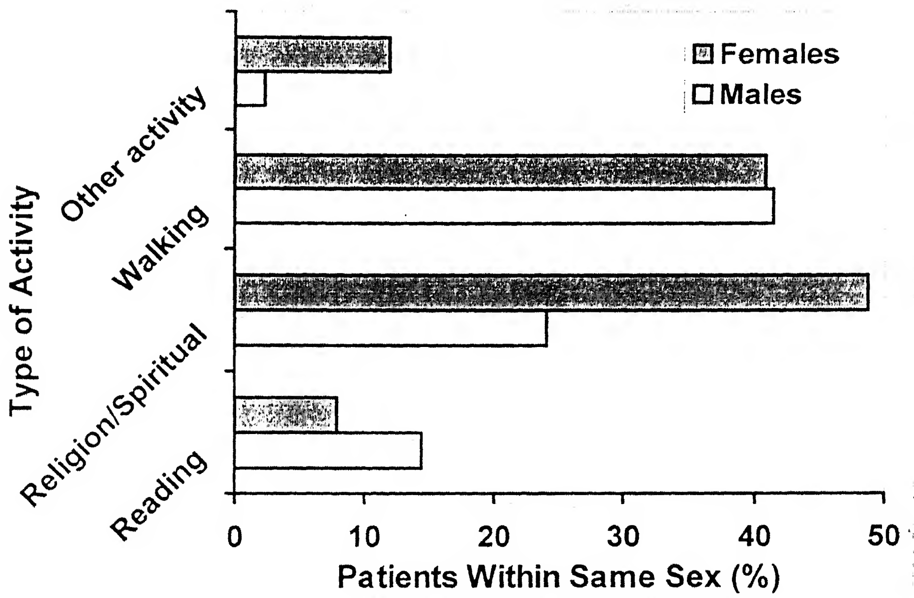

Fig. 2.6. Type of non-pharmacological ways practiced by hypertensive patients in the management of hypertension.

2.4.5.i. Patient Awareness To Disease

Ignorance, improper or no knowledge of the disease affects patient's compliance to therapy and to bring the clinically significantly symptoms under control[38,50]. From the study, we found that 52 males and 10 females (i.e., only 24.8%) affirmed that they did know about the disease picture.

2.4.5.ii. Cost

The cost of medication[31], dosing frequency[51] is a major reason for poor adherence to a regimen of anti-hypertensive medication that results in less than optimal BP control in patients. In the present study, only 39.08% males and 26.32% females were regularly taking their medication. Further queries showed 49.75% (±0.25) of both men and women felt it was unnecessary to continue the medication. Of whom, 8.3% (±0.1) felt they can take a chance, 38.85% (± 1.35) were skipping their dose deliberately for high cost of the medicines and 3.15% (±1.05) ascribed it for some other reasons, Table 2.8.

The major causes for non-compliance to drug therapy was with patients under study was (i) perception to the disease, i.e., is not necessary to continue with medication and (ii) cost factor, Fig. 2.7. The details of number of doses skipped by patients per week are given in Table 2.9, Fig. 2.8.

Table 2.8. Compliance lapse cause to follow drug regimen in hypertensive patients.

Lapse Cause	**Males**	**Females**	**Total**
Deliberately	97	48	145
Absent-mindedly	77	28	105
Reason for Deliberate Lapse			
Unnecessary to continue	48 (49.5)	24 (50)	72
Can take a chance	8 (8.2)	4 (8.4)	12
Cost factor	39 (40.2)	18 (37.5)	57
Miscellaneous	2 (2.1)	2 (4.2)	4
Values in the parenthesis are values expressed in percentage.			

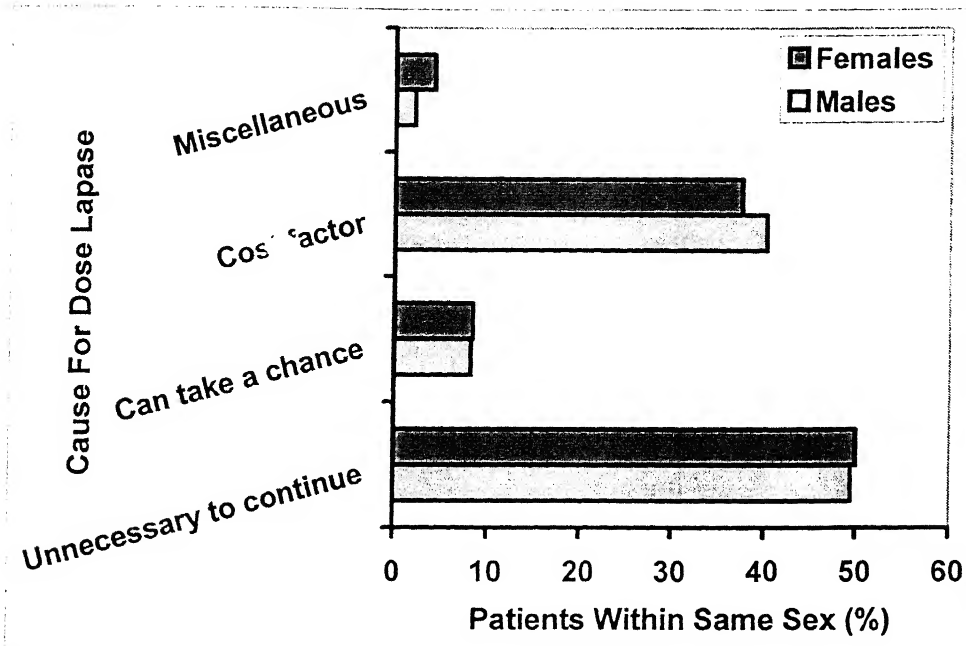

Fig. 2.7. Various causes in lapse of compliance to drug regiment in hypertensive patients.

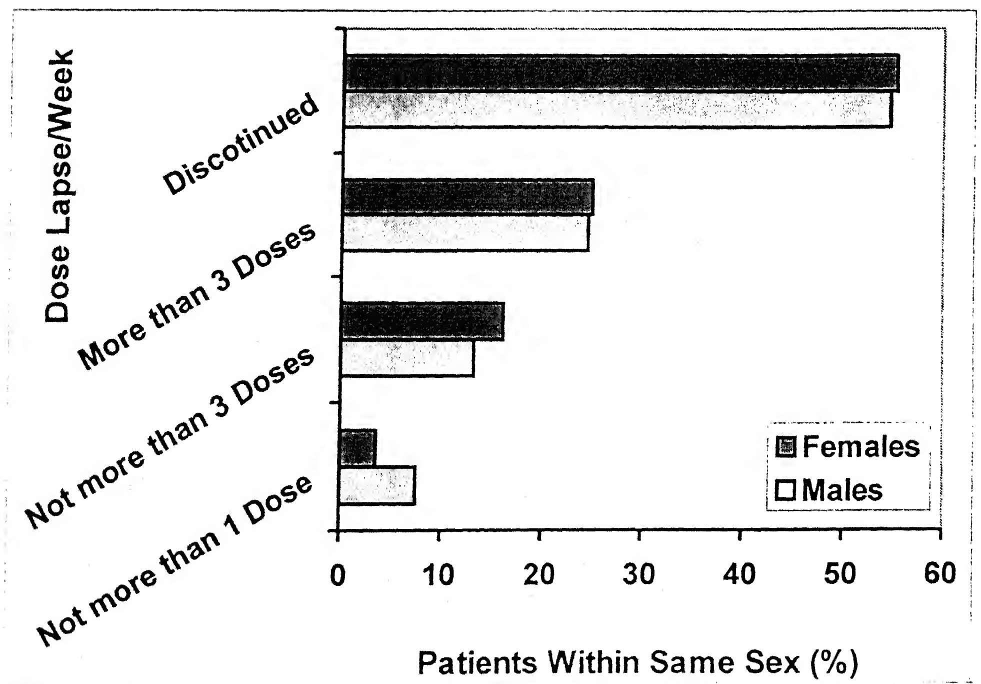

Fig. 2.8. Number of doses skipped by hypertensive patients per week.

2.4.5.iii. Dosing Schedule

When the opinion of patients for dosing schedule was sought, it was found that both 68.4% (± 0.65) males and females were quite satisfied. This fact has to be analyzed in light of the data that ~55% patients simply discontinued with the drug therapy, Table 2.9. So, is this percentage of affirmation for 2-3 times a day with drug combinations are the true projections? 30.95% (± 0.65) patients mentioned that they were not happy with the frequency of the drug therapy. This group had varied opinion for the dosing frequency, Table 2.10 and Fig. 2.9. 41% wanted once/day (23 males and 9 females) or once/two days (26 males and 6 females). As cited earlier, hypertension by itself does cause any disease but leads to manifestation of many other diseases. The survey revealed 62.4% (103 males and 43 females) hypertensive patients were found suffering from other diseases (Table 2.11 and Fig. 2.10).

Table 2.9. Actual status of non-compliance to drug therapy in hypertensive patients.

Dose Lapse / Week	Males	Females	Total
Not more than one dose	8 (7.55)	2 (3.57)	10 (6.17)
Not more than 3 doses	14 (13.21)	9 (16.07)	23 (14.19)
More than 3 doses	26 (24.53)	14 (25.00)	40 (24.70)
Discontinued	58 (54.72)	31 (55.36)	89 (54.90)
Values in the parenthesis are values expressed in percentage.			

Table 2.10. Hypertensive patients desire for dose regimen.

Desired Dose Freqency Expressed	Males	Females	Total
Once in 2 days	26 (47.27)	6 (26.09)	32 (41.00)
Once in a day	23 (41.82)	9 (39.13)	32 (41.00)
Twice in a day	6 (10.91)	8 (34.78)	14 (18.00)
Values in the parenthesis are values expressed in percentage.			

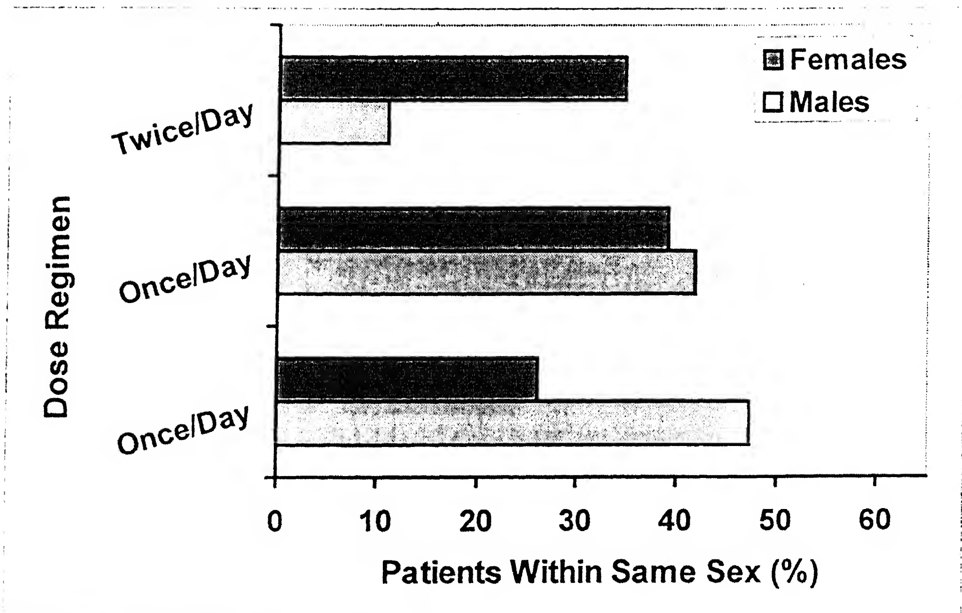

Fig. 2.9. Hypertensive patient's desire for drug dosage regimen.

2.4.6. Obesity And Hypertension

Obesity has been defined[52] as "an excess of body fat or body weight that is 20% over the ideal". The deviation from the ideal body weight for the patients was determined calculating the percentage deviation from the mid-point of upper and lower desired weight for the medium frame[53], Table 3.12. There were 11 overweight cases (14.47%) in female group, 4 cases (5.26%) by 20 - 30%, 4 more cases by (5.26%) by

Table 2.11. Other diseased afflictions in hypertensive patients.

Clinical Condition	Males	Females	Total
Diabetes	33 (32.04)	5 (11.63)	38
Kidney problem	17 (16.50)	3 (6.98)	20
Heart problem	19 (18.45)	3 (6.98)	22
Lungs	8 (8.74)	9 (20.93)	18
Miscellaneous	25 (24.27	23 (53.49)	48
Values ⁱ the parenthesis are values expressed in percentage.			

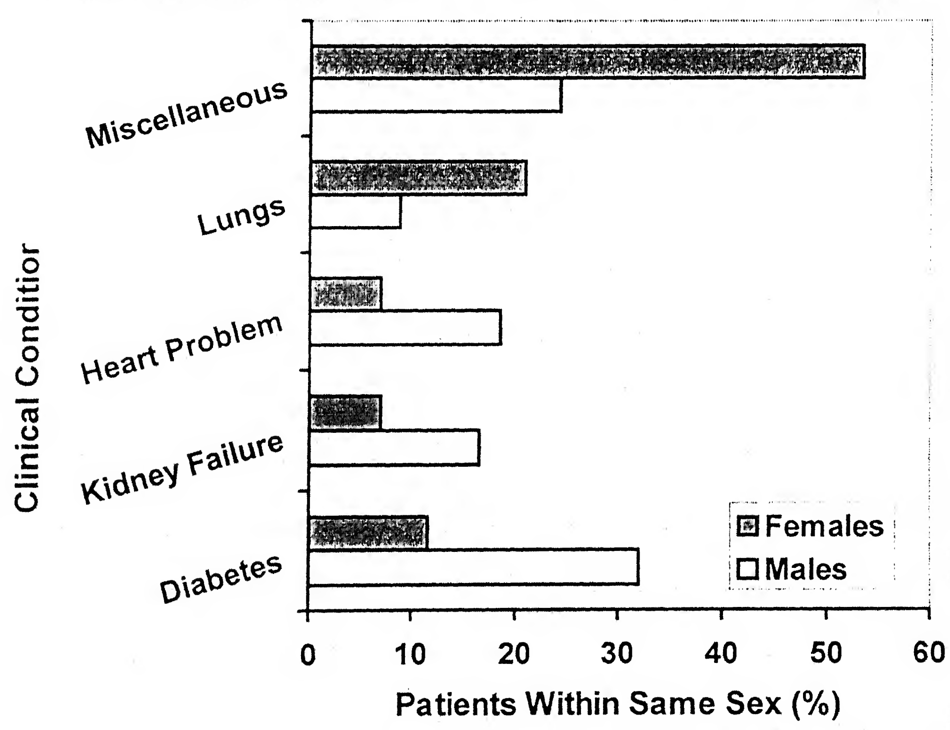

Fig. 2.10. Type of multiple diseases in hypertensive patients.

30 - 40% and 2 cases were (2.63%) by 45 – 50%, Figure 3.11. There was one unique case with 105 -110%. The present BP recorded in this case was 156/100. This patient was detected for high BP at 28 years and was 200/130. This patient is presently positive for cancer, recently undergone hysterectomy, suffering from multiple diseases (asthma, polio and effects of filiariasis). As the case was special so was the interest. On further queries, it was found that this patient was placed high in position in the government office, getting good salary. She is married and is mother of one child. She does not take the pain of putting herself to any routine any kind of physical exercise or therapy but completely depends on medication to cope with sufferings. She admits that she also sometimes deliberately skips here routine doses; is not careful about her salt intake or diet in terms of fat. All this could be ascribed to patients low morale for coping with so many diseases over years now.

In males, there were 12 (6.9%) overweight cases. 8 cases (4.6%) were over weight by 20-30%, of whom 4 were diabetic and 2 complained of having pain in left chest. 2 cases (1.15%) were over weight by 30-35%, of whom 1 was diabetic. 2 cases (1.15%) were overweight by 45-50%, of whom 1 was diabetic. The occurrence of diabetes in patients with high BP with overweight persons is 50%. The details of patients with over/underweight are given in Fig. 2.11. Overweight men in all the age group were exceeding women in all age group, seen from the upper curve maintained through out except one lady's case who was overweight by 105-110%. The reason could be women being more towards vegetarian diet[54,55] or the kinds of menial work they are involved all the time (Indian life-style is not so sophisticated and mechanized). Much of the work is done menially. The overweight group was trying to bring their body weight to ideal – a positive and active participation of patients.

Table 2.12. % Weight deviation in hypertensive patients.

Weight deviation (%)	Males	Females	Total
-30 to –25	8 (4.60)	1 (1.32)	9 (3.6)
-25 to –20	6 (3.45)	5 (6.58)	11 (4.4)
-20 to –15	13 (7.47)	11 (14.47)	24 (9.6)
-15 to –10	21 (12.07)	12 (15.79)	33 (13.2)
-10 to –5	30 (17.24)	14 (18.42)	44 (17.6)
-5 to 0	20 (11.49)	6 (7.89)	26 (10.4)
0	4 (2.30)	- -	4 (1.6)
0 to 5	31 (17.82)	6 (7.89)	37 (14.8)
5 to 10	17 (9.77)	5 (6.58)	22 (8.8)
10 to 15	6 (3.45)	3 (3.95)	9 (3.6)
15 to 20	6 (3.45)	2 (2.63)	8 (3.2)
20 to 25	3 (1.72)	1 (1.32)	4 (1.6)
25 to 30	5 (2.87)	3 (3.95)	8 (3.2)
30 to 35	2 (1.15)	2 (2.63)	4 (1.6)
35 to 40	- -	2 (2.63)	2 (0.8)
40 to 45	- -	- -	- -
45 to 50	2 (1.15)	2 (2.63)	4 (1.6)
105 to 110	- -	1 (1.32)	1 (0.4)
Values in the parenthesis are values expressed in percentage.			

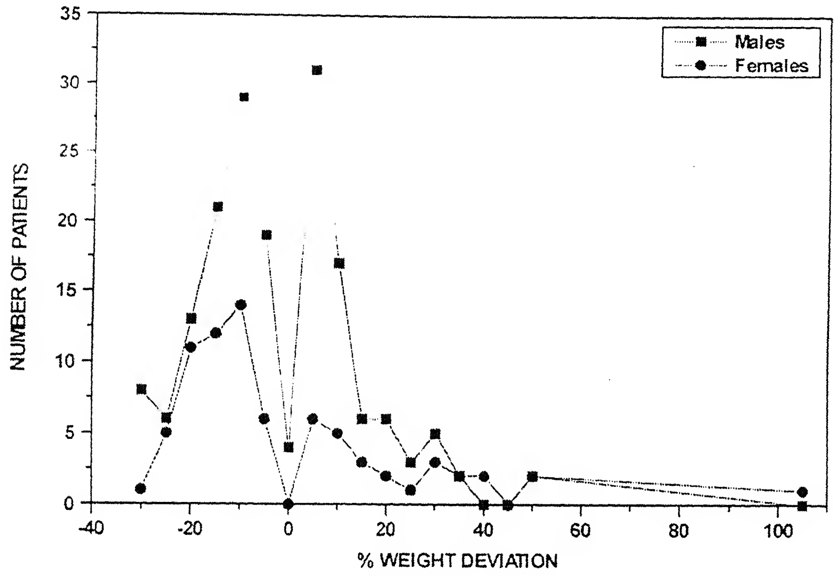

Fig. 2.11. Number weight distribution of hypertensive patients with% weight deviation.

2.4.7. Hypertension And Diabetes

There were totally 6 male diabetic cases and 2 female diabetic cases, in patients who were overweight. However, in the present study, we observed that there are 5 females and 33 males who are diabetic. The ratio of overweight diabetic to normal/underweight diabetic females was 1:2.5 while for males it as 1:5.5 – is indicative that to have a direct relationship with overweight to pronounced in females than in males.

2.4.8. Side Effects (Complains) With Hypertensive Drug Therapy

No drug therapy is free of side effects and compliments the patient's physiology. The data obtained are given in Table 2.13. The order of complains in the reducing frequency are headache, dizziness, nausea,

Table 2.13. Type of side effects found in high blood pressure patients.

Side effects	Males	Females	Total
Nausea	37 (17.28	13 (12.75)	50 (15.82)
Vomiting	15 (7.01)	14 (13.73)	29 (9.18)
Edema	12 (5.61)	7 (6.86)	19 (6.01)
Dizziness	50 (23.36)	22 (21.57)	72 (22.78)
Headache	57 (26.64)	33 (32.35)	90 (28.48)
Lethargy	16 (7.48)	9 (8.82)	25 (7.91)
None	27 (12.62)	4 (3.92)	31 (9.81)
Values in the parenthesis are values expressed in percentage.			

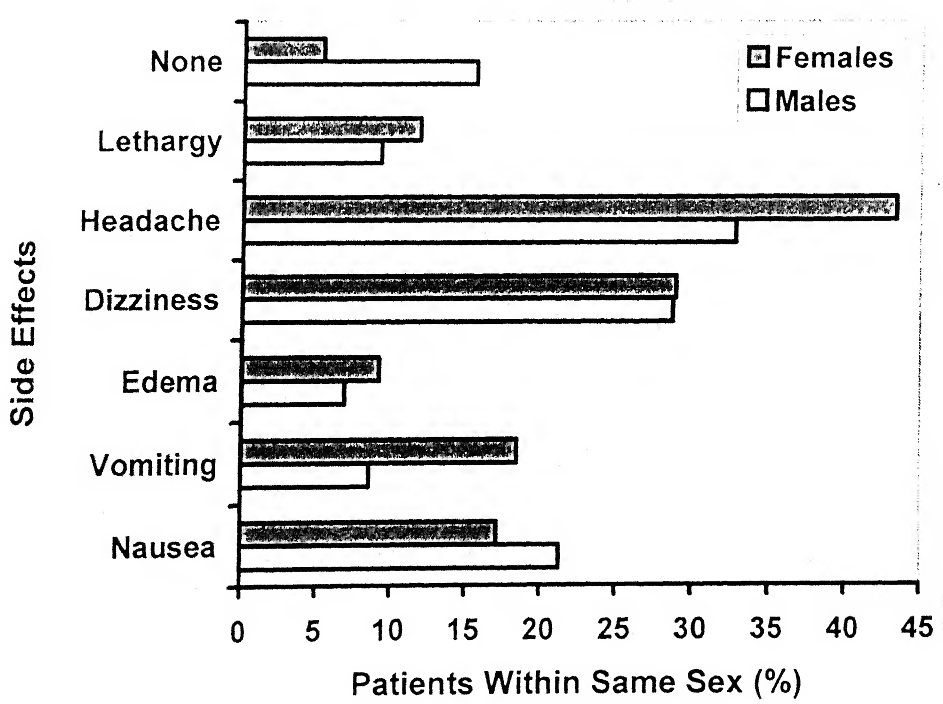

Fig. 2.12. Side effects (complains) in hypertensive patients.

2.4.8. Side Effects (Complains) With Hypertensive Drug Therapy

No drug therapy is free of side effects and compliments the patient's physiology. The data obtained are given in Table 2.13. The order of complains in the reducing frequency are headache, dizziness, nausea, vomiting, lethargy and edema, Fig. 2.12. Taking a complaint to the Physician about side effects at ones own level depends on the awareness for the disease in the patient. It was found that 26.3% females and 21.3% males did complaint to the Physician of their discomfort while the rest accepted it as conditional.

SURVEY ON HYPERTENSION QUESTIONNAIRE

S. No. _____ Date _________ ***Patient's Name*** _________________________

Age _______ ***Sex*** _______ ***Weight*** ______ ***kg*** ***Height*** _____ ' _____ "

Present BP ______________ ***Remarks***

1. When was the first blood pressure problem detected, how much recorded?
   ....

2. How did they react when they learn their blood pressure was not normal?
   - i. Could not believe ☐
   - ii. Was excepted ☐
   - iii. Makes no difference ☐

3. How much time it took for bringing down the B.P. to normal
   i. 1 month ☐ ii. 3 months ☐ iii. 6 months ☐

4. Do they know about the complete disease picture of Hypertension?
   Yes ☐ No ☐

5.i. Do they take care of their diet?
   Yes ☐ No ☐

5.ii. If yes, then control in what respect?
   - a. Salt ☐
   - b. Fat ☐
   - c. Cigarette ☐
   - d. Alcohol ☐

6. Food habits
   - a. Vegetarian ☐
   - b. Non-vegetarian ☐
   - c. Eggetarian ☐

7. What relaxation therapy they are indulged in
   - i. Reading ☐
   - ii. Religion/Spiritual indulgence ☐
   - iii. Walking ☐
   - iv. Playing ☐
   - v. None ☐

8. Do they take their medicine regularly?
   Yes ☐ No ☐

If no, number of doses missed/week.

i. Not more than one dose ☐
ii. Not more than three dose ☐
iii. More than three. ☐
iv. Discontinue ☐

9. Do they skip their medicine?

Deliberately ☐ Due to absent-mindedness ☐

If deliberately, they are doing, could it be because of

i. Felt unnecessary to continue ☐
ii. Can take a chance of skipping a dose ☐
iii. Cost Factor ☐

10. Do the patient suffer from any other diseases apart from hypertension. If yes, mentioned.

....

11. If obese, are they following any weight reducing programme.

Yes ☐ No ☐

12. What complains do they have after continuing this drug therapy?

i. Nausea ☐
ii. Vomiting ☐
iii. Edema ☐
iv. Dizziness ☐
v. Headache ☐
vi. Itching ☐
vii. Others ....

13. Have they shared this complain with their Physician.

Yes ☐ No ☐

14. How do the patient react for frequency of dosing

Satisfactory ☐ Not satisfactory ☐

15. If not satisfactory, would they like to have -

i. Once a day ☐
ii. Twice a day ☐
iii. Three times a day ☐

- End -

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Chapter 3

Pharmacopoeial Evaluation of 50 mg Immediate Release Marketed Metoprolol Tartrate Tablets ...

3.1. INTRODUCTION

The most significant impediments to keeping patients healthy and curing disease is noncompliance with prescribed medication regimens[1], especially in long-term continual therapy[2,3]. From our study carried out for people suffering from hypertension, Chapter 2 of this thesis, it was found that 38.85% (±1.35) population was skipping their dose deliberately for high cost of medicines; only ~40% male and ~26% females were regularly taking medicines. With rising healthcare cost, Indian government is putting efforts to favor the prescription of generic drugs and it is expected that drugs worth US $ 31 billion is to face patent expiry in years leading to 2010[4].

Generic drug products are considered to be cheap therapeutically equivalent to the brand name product whose patents have been expired[5-6]. The topic has been dealt in detail, in Chapter 1.

3.2. OBJECTIVE

3.2.1. To comparatively evaluate 50 mg immediate release (IR) metoprolol tartrate tablets from different manufacturers available in the Indian market to USP 27 NF 22 specifications.

3.2.2. To estimate the projected ,cost of the drug therapy for each product for one year based on the usual dosage regimen.

3.3. EXPERIMENTAL STUDIES

3.3.1. DOSAGE FORM CHARACTERIZATION - UNOFFICIAL TESTS

3.3.1.i Organoleptic Properties

Shape & Color: Visual inspection under magnifying glass.

Size determination: Digimatic Micrometer, Mitutoyo, Japan, with ± 0.001mm accuracy.

3.3.1.ii. Test for Friability

Equipment: Electorlab EF-2 Friabilator, USP, Mumbai.

Tablet Quantity: ~7 gms of tablets.

Tolerance: Not more than 1% after 100 revolutions.

3.3.1.iii. Crushing strength (Hardness Test)

Equipment: Tablet Hardness Tester, Pfizer Type (with 0.1 kg accuracy).

Number of Units: 06 (Average value)

3.3.2. OFFICIAL TESTS AND SPECIFICATIONS

3.3.2.i. Test for Weight Variation

Equipment: Precisa XB 220 A (with 0.0001 gm accuracy).

Number of Units Weighed: 10.

Tolerance: Amount of the active ingredient in each of the 10 dosage units lies within the range of 85.0% to 115.0% of the label claim assuming homogeneous distribution of the active ingredient; and the relative standard deviation is less than or equal to 6.0%.

3.3.2.ii. Test for Drug Content Uniformity

Equipment: Pharma Spec UV1700 UV Visible Spectrophotometer, Japan.

Number of Units Assayed: 10.

Assay: UV Spectrophotometric at 275 nm in distilled water.

Tolerance: Amount of the active ingredient in each of the 10 dosage units lies within the range of 85.0% to 115.0% of the label claim and the relative standard deviation is less than or equal to 6.0%.

3.3.2.iii. Disintegration

Equipment: Electrolab ED-2 Disintergration Tester, USP, Mumbai.

Number of Units: 06.

Medium: 1000 mL Distilled water.

Temperature: 37 ^{o}C (± 2).

Tolerance: No part of the tablet retained on the screen; if, then the residual mass is not palpable.

3.3.2.iv. Dissolution Test Conditions

Equipment: Electrolab TDT-08L Dissolution Tester, USP, Mumbai.

Number of units to be tested: 06.

Medium: Simulated gastric fluid (without enzyme; 900 mL.

Apparatus 1: 100 rpm maintained at 37 ^{o}C (± 0.5).

Time: 30 mins.

Tolerance: Not less than 75% (Q) of the labeled amount of drug dissolved in 30 mins.

3.4. PRODUCTS

The following products with their batch details were used in the study.

3.4.1. Betoloc® 50

R_x Metoprolol Tartrate Tablets IP
Each uncoated tablet contains Metoprolol Tartrate IP 50 mg.
Dosage: As directed by the Physician.
Precaution: Schedule H drug.
Warning: To be sold by retail on the prescription of a Registered Medical Practitioner only.

Storage: Protect from light.
Manufacturing License Number: NB-182/81
Batch Number: BTF DO42
Manufacturing date: 10/2003
Expiry date: 09/2007
Retail Price: Not to exceed Rs. 23.53 for 10 tablets. Local Taxes Extra.
Manufactured by: AstraZeneca Pharma India Ltd, 12th Mile, Bellary Road, Bangalore – 560 063.

3.4.2. Lopressor® 50

R_x Metoprolol Tartrate Tablets IP

Each uncoated tablet contains Metoprolol Tartrate IP 50 mg.
Dosage: As directed by the Physician.
Precaution: Schedule H drug.
Warning: To be sold by retail on the prescription of a Registered Medical Practitioner only.
Storage: Protect from light.
Manufacturing License Number: PD-132.
As per formula licensed by Novartis India Ltd.
Batch Number: 43002V
Manufacturing date: May 2004
Expiry date: Apr. 2008
Retail Price: Not to exceed Rs. 24.50 for 10 tablets. Local Taxes Extra.
Manufactured by: Emcure Pharmaceutical Ltd., C-10(12), FunctionalElectronic Estate, M. I D.C., Bhosari, Pune 411 026, India.

3.4.3. Metapro™ - 50

R_x Metoprolol Tartrate Tablets IP

Each uncoated tablet contains Metoprolol Tartrate IP 50 mg.
Dosage: As directed by the Physician.
Precaution: Schedule H drug.
Warning: To be sold by retail on the prescription of a Registered Medical Practitioner only.
Storage: Keep in a cool dry place.
Manufacturing License Number: 300
As per formula licensed by Novartis India Ltd.
Batch Number: MTP-008
Manufacturing date: Oct. 2003
Expiry date: Sep. 2005
Retail Price: Not to exceed Rs. 17.00 for 10 tablets. Local Taxes Extra.
Manufactured by: MICRO LABS LIMITED, 92, SIPCOT Industrial Complex, HOSUR – 635120 (T.N.)

3.4.4. METO – 50

R_x Metoprolol Tartrate Tablets IP

Each uncoated tablet contains Metoprolol Tartrate IP equivalent to 50 mg.
Dosage: As directed by the Physician.
Precaution: Schedule H drug.
Warning: To be sold by retail on the prescription of a Registered Medical Practitioner only.
Storage: Protect from light.
Manufacturing License Number: 1488 A
Batch Number: MOB 103
Manufacturing date: Jan. 2003
Expiry date: Dec. 2006
Retail Price: Not to exceed Rs. 18.40 for 10 tablets. Local Taxes extra.
Manufactured by: Biotrans Pharmaceutical Pvt. Ltd., 3 New Natara- puram, 2nd Street, M.M.D.A. colony, Anumbakkam, Chennai – 600 106.
Marketed by: Mano Pharmaceuticals Pvt. Ltd., 447, poonamallee, High Road, Chennai – 600 029.

3.4.5. Metolar - 50

R_x Metoprolol Tartrate Tablets IP

Each uncoated tablet contains Metoprolol Tartrate IP 50 mg.
Precaution: Schedule H drug.
Warning: To be sold by retail on the prescription of a Registered Medical Practitioner only.
Manufacturing License Number: 366
Batch Number: T40171
Manufacturing date: Jun. 04
Expiry date: May 07
Retail Price: Not to exceed Rs. 20.50 for 10 tablets. Local Taxes Extra.
Manufactured by: MEDITAB SPECIALITIES PVT. LTD, 352 Kundaim Indl EstateGoa 403 115 Under the technical guidance of CIPLA LTD.

3.5. RESULTS AND DISCUSSION

3.5.1. Unofficial Tests

Two of the five products were blister form while others opted for strip packed. All the five products were uncoated, circular in color, colorless, but carried distinction/identification in terms of presence or absence of (i) beveled edges, (ii) engraved symbols, (iii) flat/convex surface and (iv) scored. Out of 5 products, 3 products were with ~0.8 cm in diameter and ~0.33 cm thickness but the maximum diameter of the tablet was ~0.9 cm with maximum thickness of ~0.35 cm. The

friability values for all the tablets was less than 1% while the hardness/crushing strength values varied from 0.53 to 5.57 kg/cm^2. The details of which are given in Table 3.1. and 3.2.

Table 3.1 Packaging properties and appearance of various marketed 50 mg IR release metoprolol tartrate tablet.

Product	**Packaging**	**Appearance**
IR-A	Blister	Uncoated, white, circular, biconvex, scored on one side with engraved symbols 'A' & 'B' on same side. Back side plane.
IR-B	Strip	Uncoated, white, circular, biconvex, scored on one side with engraved symbols 'H' & 'M' on same side. On the other side engraved with symbol 'CG'.
IR-C	Strip	Uncoated, white, circular, flat with beveled edges at top and bottom.
IR-D	Blister	Uncoated, white, circular, flat with one surface beveled edged.
IR-E	Strip	Uncoated, white, circular, biconvex, scored on one side with beveled edges & engraved on the other side engraved with symbol 'MT'.

Table 3.2. Dimensional size, hardness and friability values in various marketed 50 mg IR metoprolol tartrate tablet.

Product	Dimension		Hardness (kg/cm^2)	Friability (%)
	Diameter (cm)	Thickness (cm)		
IR-A	0.807 (0.001)	0.325 (0.001)	5.57 (0.56)	0.0623
IR-B	0.910 (0.001)	0.357 (0.001)	5.60 (1.17)	0.3347
IR-C	0.800 (0.001)	0.268 (0.001)	5.12 (1.50)	0.7568
IR-D	0.888 (0.002)	0.338 (0.001)	0.53 (0.05)	0.0520
IR-E	0.800 (0.001)	0.263 (0.001)	1.68 (0.19)	0.0357

* Values in the parenthesis indicate the standard deviation estimated from 6 separate tablets.

3.5.2. Official Tests And Specifications

All the marketed products of metoprolol tartrate qualified the official tests with the values within the specified limits. The values are given in Table 3.3. and fig. 3.1, 3.2, 3.3 and 3.4; ,hich are self-explanatory. A close look at the data and the respective graphs indicate that all the tablets weight were highly consistent but was not so in IR-D coded tablet; so also the values in content uniformity test. The disintegration values were very much consistent in products coded IR-A, IR-B and IR-C, while for the amount of drug released at the end of 30 minutes were highly consistent for all the coded product except IR-C.

Table 3.3. Various official test result data on different marketed 50 mg immediate release metoprolol tartrate tablet.

Product	Weight Variation (% Active Content)	Content Uniformity (Actual % Active Content)	Disintegration Test (mins)	Drug Dissolved at T_{30} (min) (% Q)
IR-A	110.04 (1.26) [a]	110.04 (1.75) [a]	11.50 (0.11) [b]	109.68 (1.44) [b]
IR-B	110.04 (0.81) [a]	110.04 (1.17) [a]	9.23 (0.05) [b]	109.85 (0.79) [b]
IR-C	109.44 (3.06) [a]	109.57 (3.24) [a]	5.23 (0.11) [b]	109.14 (3.51) [b]
IR-D	110.85 (1.072) [a]	110.85 (3.26) [a]	1.51 (0.20) [b]	110.42 (1.07) [b]
IR-E	109.42 (109.42) [a]	109.42 (1.96) [a]	6.41 (0.35) [b]	109.19 (1.63) [b]

* Values in the parenthesis indicate the standard deviation estimated on [a] 10 and [b] 6 separate tablets respectively.

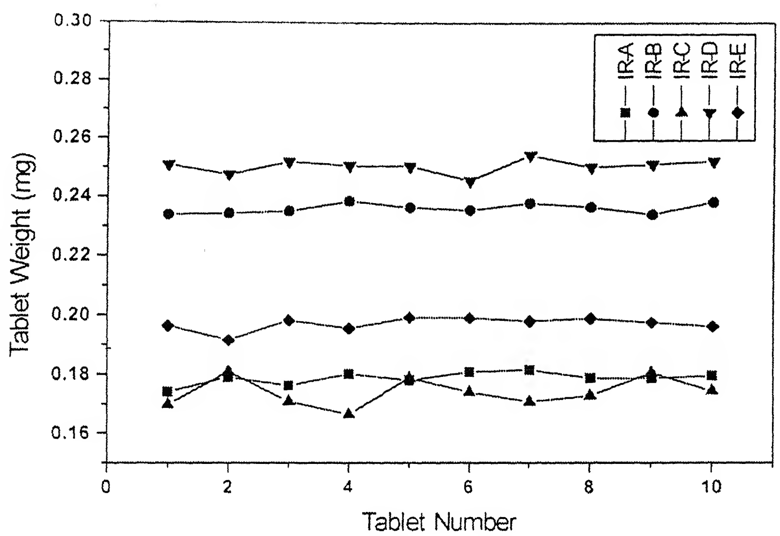

Fig.3.1. Weight variation test values for the marketed product.

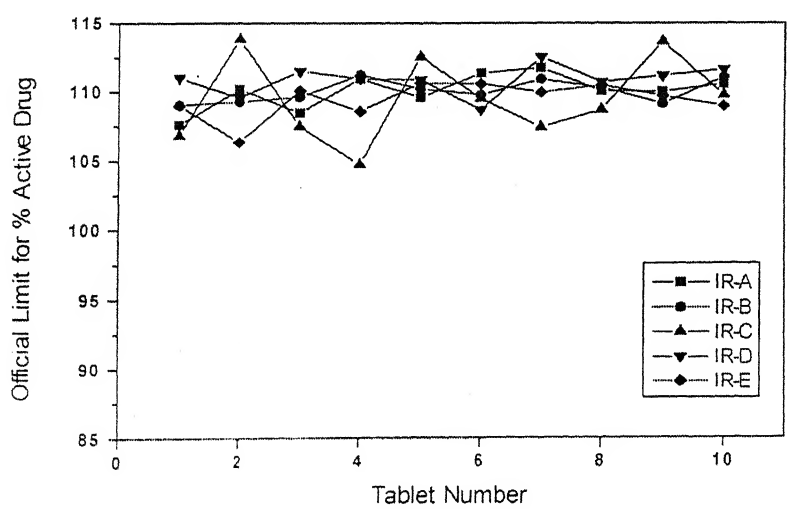

Fig.3.2. Content uniformity test values for marketed product.

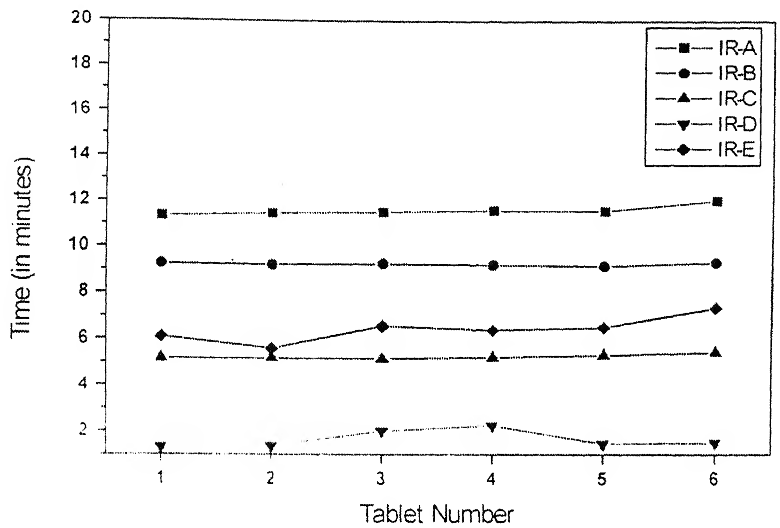

Fig.3.3. Disintegration test value for marketed product.

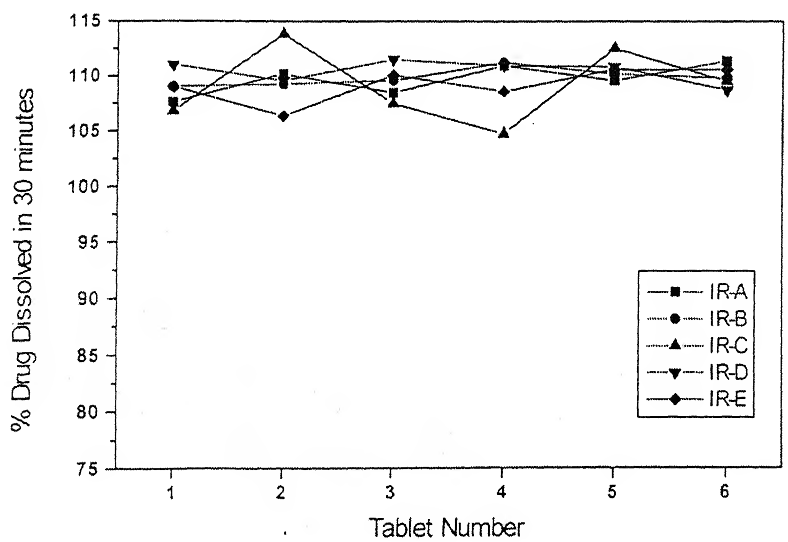

Fig. 3.4. In vitro dissolution test at T_{30} for marketed product.

Table 3.4. Cost of different marketed IR 50 mg marketed metoprolol tartrate tablet.

Product	Cost for 10 Tablets (in Rupees)	Cost for 1 year (in Rupees)	
		Once/Day	Twice/Day
IR-A	23.53 (+ 38.15%)	858.85 (238.35)	1717.69 (476.69)
IR-B	24.50 (+ 44.12%)	894.25 (273.75)	1788.50 (547.50)
IR-C	17.00 (0%)	620.50 (0)	1241.00 (0)
IR-D	18.40 (+ 08.24%)	671.60 (051.10)	1343.20 (102.20)
IR-E	20.50 (+ 20.59)	748.25 (127.75)	1496.50 (255.50)

* Values in the parenthesis indicate the difference in cost from the lowest priced product.

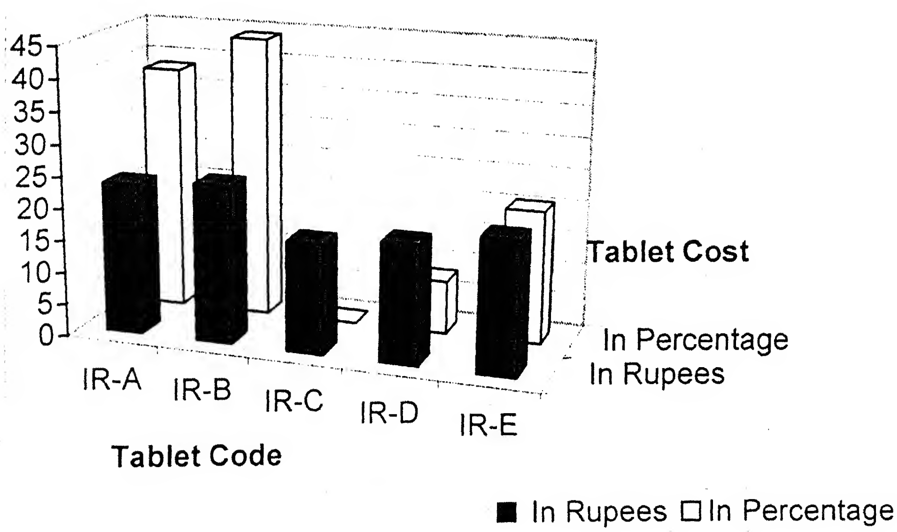

Fig.3.5. Estimated cost projection in different marketed IR 50mg metoprolol tartrate tablet.

3.5.3. Cost Evaluation

Life style drugs like metoprolol tartrate and other hypertensive drugs are generally prescribed once or twice in a day. Hence, the cost projection incurred by the patient for 1 year when taken once/twice a day are estimated in all the five marketed products. The data is given in table 3.4. (fig.3.5). The product cost found in increasing prices is: IR-C < IR-D < IR-E < IR-A < IR-B. When the cost difference in % was estimated, a difference of ~ 44% was found between the cheapest and the costliest product.

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Chapter 4

General Introduction...

4.1. DRUG DELIVERY SYSTEM

Most drugs today are still prescribed in dosage forms that date back to the earliest records of practice of pharmacy; the pill (1500 BC); the coated pill (900 AD); the tablet (10th century); and the capsule (1983). Progress in pharmaceutical technology, since the inception of such a discipline (late 1800s and early 1900s), emphasized the development of high speed processing equipment. The functional characteristics of a dosage form attracted little attention until the unfolding of the 70s[1].

The 20th century has witnessed great strides in the management of various pathological conditions with the discovery of increasingly sophistication and potent drug molecule such as antibiotics, steroids, peptides and proteins[2]. Significant advances in controlled drug delivery have been achieved and several products have enjoyed commercial success, past 25 years. And now, the concept of controlled release technology has entered the public's consciousness and reasonable resources have been committed to the field by both the pharmaceutical industry and government agencies.

All over the world, the novel Controlled Drug Delivery System (CDDS) is growing as one of the frontiers in pharmaceutical technology. Over the past 30 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of CDDS, greater attention has been focused on its development[3].

4.2. DEFINITIONS

Attempts to control the time course and specificity of drugs within the body have led to the development of several drug modifications and dosage forms[2]. Different definitions/ terminologies have emerged in this new area of CDDS[4-6]:

Conventional Drug Delivery is a technique to deliver therapeutic agents into human body whereby therapeutic agent is immediately available for action and where no mechanism is incorporated in the system, which will modulate the release. This includes immediate release tablets, capsules, injectables, ointments and creams.

New Drug Delivery System(s) (NDDS) are techniques capable of modifying the rate of drug delivery, altering the duration of action and or targeting the delivery of drug to the tissue.

Extended-Release Systems include drug delivery system such as sustained release, controlled release, time released, prolonged release that achieves prolonged therapeutic effect by continuous release of drug over an extended period of time after single administration. The release rate and site of delivery may be predefined in certain extended release system.

Controlled-Release System are drug delivery systems which provide some control, whether temporal or spatial nature or both, on drug release in the body, or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells. If it is unsuccessful at this, but nevertheless prolongs therapeutic blood or tissue levels of the drug for an extended period of time, it is considered a **Prolonged-Release System**.

Delayed-Release Systems are those that use repetitive, intermittent dosing of drug from one or more immediate release units incorporated into single dosage form. A delayed release dosage form does not produce or maintain uniform drug blood levels within the therapeutic range, but, nonetheless, is more effective for patient compliance than conventional dosage forms.

Site Specific And Receptor Release refer to targeting a drug directly to a certain biological location. In the case of site specific release the target is adjacent to or in the diseased organ or tissue. For receptor release, the target is the particular receptor for a drug within an organ or tissue. Both of these systems satisfy the spatial aspect of drug delivery.

4.3. EXTENDED VS CONVENTIONAL DRUG DELIVERY[7]

Consider a single dosing of a hypothetical drug that follows a simple one-compartment pharmacokinetic model for disposition. Depending on the route of administration, a conventional dosage form of the

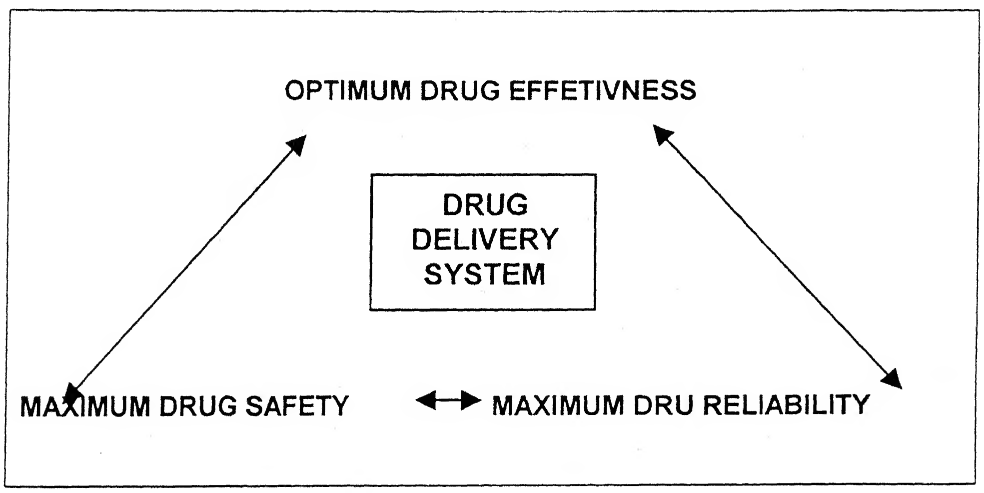


Fig. 4.1. Requirement of drug delivery system.

drug, e.g., a solution, suspension, capsule, tablet, etc., probably will produce a drug blood level versus time profiles to that shown (fig. 4.2) It can be seen from this figure that administration of a drug by either intravenous injection or an extra route does not maintain drug levels with in therapeutic range for extended periods of time. The short duration of action is due to the inability of conventional dosage forms to control temporal delivery. If attempts is made to maintain drug blood levels in the

therapeutic range for longer periods by, for example, increasing the initial dose of an intravenous injection, as shown by the dotted line in the fig. 4.2, toxic levels may be produced at early times. This approach obviously is undesirable and unsuitable. An alternate approach is to administer the drug repetitively using a constant dosing interval. This is shown in fig.4.3 for oral route. In this case, the drug blood level reached and the time required to reach that level, depends on the dose and the dosing interval. There are several potential problems inherent in multiple-dose-therapy.

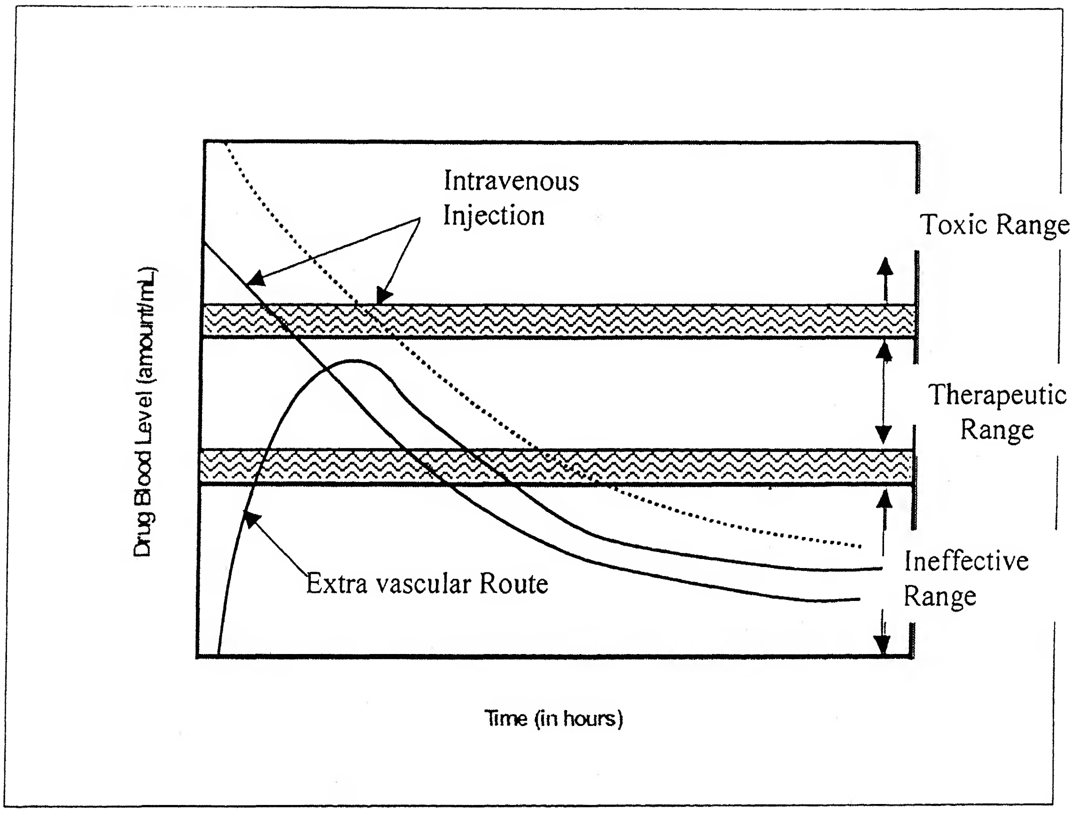


Fig. 4.2. Drug blood level versus time profile for intravenous (I. V.) and extra vascular (E.V.) route.

If the dosing interval is not appropriate for the biological half-life of the drug, large "peaks" and "valleys" in the drug blood level may result. For example, drugs with short half-lives require frequent dosing to maintain constant therapeutic levels.

- The drug blood level may not be within the therapeutic range at sufficiently early times, an important considerations for certain diseased states.
- Patient non-compliance with multiple dosing regimens can result in failure of this approach.

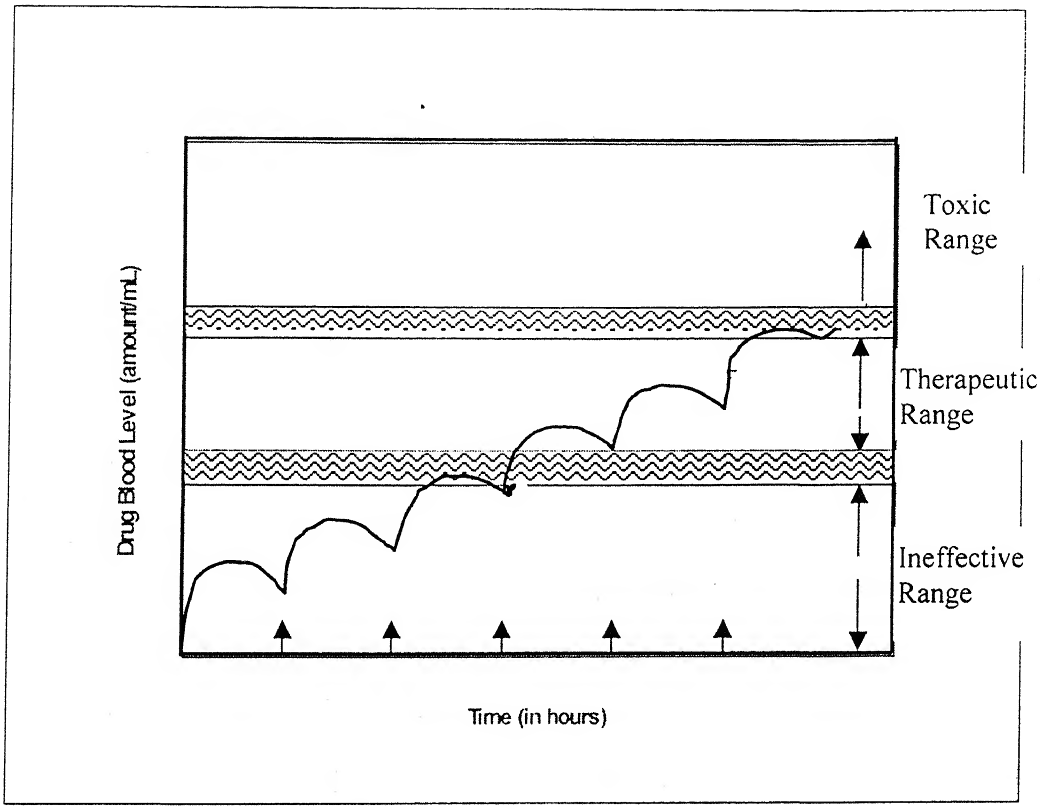


Fig. 4.3. Drug blood level versus time profile from the multiple dose oral therapy.

Frequently, these problems are significant enough to make drug therapy with conventional dosage forms less desirable. This fact, coupled with the intrinsic inability of conventional dosage forms to achieve spatial placement, is a compelling motive for investigation of extended release drug delivery systems.

Conventional dosage forms can be considered to release their active ingredients into an absorption pool immediately. This is illustrated in the following simple kinetic scheme.

$$\text{Dosage Form} \xrightarrow{k_r} \text{Absorption Pool} \xrightarrow{k_a} \text{Target Area} \xrightarrow{k_{el}}$$

drug release *absorption* *elimination*

The absorption pool represents solutions of the drug at the site of absorption and the terms k_r, k_a and k_{el} are first order rate constants for drug release, absorption and overall elimination respectively. Immediate release from a conventional dosage form implies that $k_r >>> k_a$ or, alternatively that absorption of drug across a biologica l membrane such as the intestinal epithelium is the rate limiting step in delivery of the drug to its target area. For non-immediate release dosage forms $k_r <<< k_a$, i.e., release drug from the dosage form is the rate limiting step. This causes the above kinetic scheme to reduce to

$$\text{Dosage Form} \xrightarrow{k_r} \text{Target Area} \xrightarrow{k_{el}}$$

drug release *drug elimination*

Essentially, the absorption phase of the kinetic scheme becomes insignificant compared to the drug release phase. Thus, the effort to develop a non-immediate release drug delivery system must be directed altering the release rate by affecting the value of k_r. The ways in which this has been attempted are discussed later in this chapter.

4.4. RATIONALE OF EXTENDED RELEASE (ER) DRUG DELIVERY SYSTEM (DDS)

The basic rationale for extended drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacologically active moieties, by using novel drug delivery system by modifying the molecular structure and / are physiological parameters inherent in selected route of administration. It is desirable that the

duration of drug action becomes, more a design property of a rate controlled dosage form and less, are not at all a property of a drug molecule's inherent kinetic properties. Thus, optimal design of extended release systems necessitates a thorough understanding of the pharmacokinetics and pharmacodynamics of the drug.

The primary objective of extended drug delivery is to ensure safety and to improve efficacy of drug as well as patients compliance. This is achieved by better control of plasma drug levels and less frequent dosing.

For conventional dosage form, only the Dose (*D*) and dosing Interval (*T*) only can be varied and for each drug, there exists a therapeutic window of plasma concentration, below which, therapeutic effect is insufficient and above which undesirable are toxic side effects are elicited. As an index of this window, the Therapeutic Index (*TI*) can be used. This is often defined as the ratio of median Lethal Dose (LD_{50}) to median Effective Dose (ED_{50}). Alternatively, it can be defined as the ratio of maximum drug concentration (C_{max}) in blood that can be tolerated to the minimum concentration (C_{min}) needed to produce an acceptable therapeutic response.

In general, the dosing interval may be increased either by modifying the drug molecule to decrease the rate of elimination (k_{el}) or by modifying the release rate of a dosage form to decrease the rate of absorption (k_a). Both approaches seek to decrease fluctuations in plasma levels during multiple dosing, allowing the dosing interval to increase without either overdosing or under dosing. When attempting to extend the dosing interval by decreasing the rate of absorption, the formulator will be confronted with the physiological constant of a finite residence time at the absorption site. For example, an effective absorption time for orally administered drugs is about 9-12 hour. If the rate of absorption decreases too much, some of the unabsorbed drug will pass into the large intestine, where absorption is slower and more variable

and where bacterial degradation of the drug may occur. Thus, drugs with half-lives of 6 hour or less and possessing therapeutic indices less than 3 must be given not less frequently than every 12 hour[8]. Unless gastrointestinal transit can be lengthened, once daily orally dosing may prove to be difficult to achieve for drugs with such extremely short half lives[9].

4.5. NEW DRUG DELIVERY SYSTEM

The term drug delivery covers a very broad range of techniques used to get therapeutic agents into the human body. In the recent years, several technical advancements have been made resulting in the development of New Drug Delivery Systems (NDDS). These techniques are capable of modifying the rate of drug delivery, altering the duration of action and or targeting the delivery of drug to the tissue[10]. This is evidenced by general texts and review articles published in this subject[11-14].

New drug delivery systems have been a topic of great interest due to various possibilities:

- Possibility of patenting successful drug by applying the concepts and techniques of new drug delivery, eg. Ciprofloxacin OD.
- The enormous costs in bringing new drug entity successfully to the market have encouraged the development of NDDS.
- New systems are required to deliver novel, genetically engineered pharmaceuticals like peptides and proteins to the site of action; without incurring significant immunogenicity or biological inactivation.
- Treatment of enzyme deficient diseases and cancer can be improved by better targeting.

- Therapeutic efficacy and safety of the drugs administered by conventional methods can be enhanced by more, special and temporal placement with in the body, thereby reducing the strength and number of doses administered.
- NDDS is the phasing of the drug administered to the need of the conditions at hand so that an optimal amount of drug is used to cure or control the condition in minimum time.
- Research in new drug delivery during the last decade has resulted in an increase in the sophisticated means to sustain the delivery of drugs.

4.5.1. Possible Potential Advantages Of NDDS

Several authors[15-16] have cited different reasons for attempting to modify action of drug. The potential advantages are as follows-

- Eliminate fluctuations in drug level, which are inevitable in conventional dosage forms where efficacy of drug is decreased which can be avoided with the use of NDDS.
- Patient acceptance of the product when compared to the conventional dosage form is increased due to decrease in frequency of administration, thus important patient compliance.
- In a multiple conventional dosage form, the dose of the drug being administered is too high which can be reduced by administration as NDDS.
- Nighttime dosing can be avoided without reducing the therapeutic efficacy, which is inevitable with conventional dosage forms, e.g. Diltiazem, Salbutamol.
- The severity or frequency of untoward effects sometimes may be reduced by administration of NDDS, e.g. Controlled release Ibuprofen.
- By minimizing the fluctuation of drug levels in the biological fluids a better management of diseases can be achieved.

4.5.2. Possible Limitations Of NDDS[17]

- Higher cost of production.
- Failure of systems: which may lead to accidental poisoning resulting in dose dumping or one where in no drug is released at the site of action.
- Size of dosage form may be big and hence may be a problem in case of geriatric patients (i.e., ability to swallow).
- Intra patient variation in absorption, distribution, metabolism and elimination of drug.
- NDDS cannot be administered when precision is required.
- Drugs whose biological half life ($t_{½}$) is long and self-prolonged and or blood levels of drugs with erratic patterns are not suitable for prolonged release formulation.

4.5.3. Different Avenues In NDDS

Current state of art is witnessing a revolution in new techniques for drug delivery. These techniques are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and /or targeting the drug to specific tissue. These advancements led to the development of several novel drug delivery systems, which have been effectively applied to overcome the various drawbacks of conventional drug delivery.

The various avenues of NDDS include:

- Oral drug delivery and delivery systems.
- Mucosal drug delivery system, which encompasses the potential routes of non-invasive systemic administration.
- Nasal drug delivery systems.
- Ocular drug delivery systems.
- Transdermal drug delivery systems.

- Parenteral drug delivery systems.
- Vaginal drug delivery systems.
- Intrauterine drug delivery systems.
- Systemic delivery of peptide based pharmaceuticals.

4.6. THERAPEUTIC SYSTEMS

Heilmann coined a new term "Therapeutic System" to include a new route for drug administration and delivery to target organ. A therapeutic system[18-19] is a drug containing preparation or dosage from that released one or more drugs continuously in a predetermined pattern for a fixed period of time either systemically or to a specified target organ. Therapeutic systems may release the drug at a constant rate (zero order) or at a predictably constant declining rate (first order) for a certain period of time.

4.6.1. COMPONENT OF A THERAPEUTIC SYSTEM

A therapeutic system consists of four components (fig. 4.4)

A. The drug or drugs.

B. The drug delivery module.

C. The platform.

D. The therapeutic program.

4.6.1.A. DRUG

The drug is one of the several components in a therapeutic system. The choice of drug is with regard to its proven efficacy, pharmacokinetic behavior and its physicochemical characteristics.

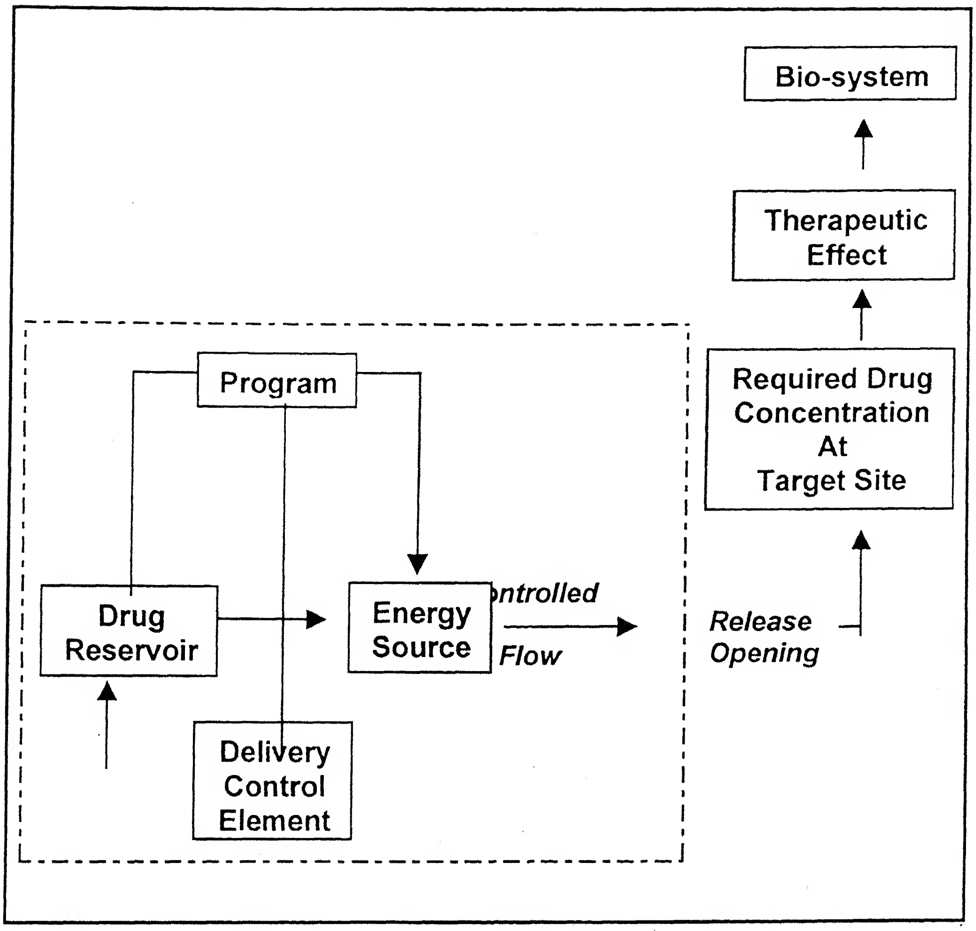


Fig. 4.4. Therapeutic systems with open control loop.

4.6.1.B. DRUG DELIVERY MODULE

This is contained in the platform or carrying element. It is responsible for releasing the drug according to a predetermined therapeutic program. It consists of four elements:

(i) Drug Reservoir: A single or multi-chambered element that stores the compound in a stable form. Theoretically, the dimensions of reservoir may be of any size except the capacity of a target organ (such as conjunctival sac) imposes limitations on size.

(ii) Control Element: A control element is responsible for the programmed release pattern.

(iii) Energy Source: An energy source for providing an impetus for the transport of the drug molecule from the reservoir to the biological medium that first receives the drug.

(iv) The drug must leave the system via the release opening or surface before it can arrive at the pre-selected target organ in the bio-system. The size and shape of the opening or surface may differ from system to system.

4.6.1.C. PLATFORM

All the elements of a therapeutic system are integrated into the platform (carrying element) to form the functional unit, which comes into contact with the bio-system.

4.6.1.D. THERAPEUTIC PROGRAM

The program contained in the therapeutic system is designed to meet a specific therapeutic need by maintaining optimal drug levels over a defined time period.

A therapeutic system provides for a release of a drug by use of a controlled source of energy. As an energy source, physicochemical energy (like diffusion, osmosis and dissolution / chemical reaction), mechanical energy (by the use of elastomers and pumps) and electrical or nuclear energy may be used.

4.6.2. CLASSIFICATION OF THERAPEUTIC SYSTEM

A therapeutic system may be accomplished through several routes of administration, e.g. oral, transdermal, nasal, ocular, rectal, subcutaneous implantation and intramuscular injection. Moreover, numerous technologies have been used

successfully to control the systemic delivery of drug. Therapeutic system can be classified into two major categories.

A. Non-biofeedback controlled drug delivery.

B. Bio-feedback controlled drug delivery.

4.6.2.A. NON-BIOFEEDBACK CONTROLLED DRUG DELIVERY SYSTEM

Non-biofeedback controlled therapeutic system has three components – (i) the drug or drugs, (ii) delivery module and (iii) the platform. A non-biofeedback controlled system releases the drug from the delivery systems in predictable manner either first order or zero order rate or can be designed to release the drug at specific rate or site. It can be passive preprogrammed or active preprogrammed. These drug delivery systems (DDS) are further classified depending on the release controlling mechanism[20-22].

4.6.2.A.i. Diffusion Controlled Drug Delivery System

In these systems, the release rate of drug is determined by its diffusion through a water insoluble or hydrophilic polymer. There are basically two types of diffusion devices: reservoir devices (fig. 4.5) in which a core of drug is surrounded by a polymeric membrane and matrix devices in which dissolved or dispersed drug is distributed uniformly in an inert polymeric matrix.

4.6.2.A.i.a. Reservoir Systems[23-25]

These dosage forms consists of a core of a drug surrounded by a polymeric membrane.

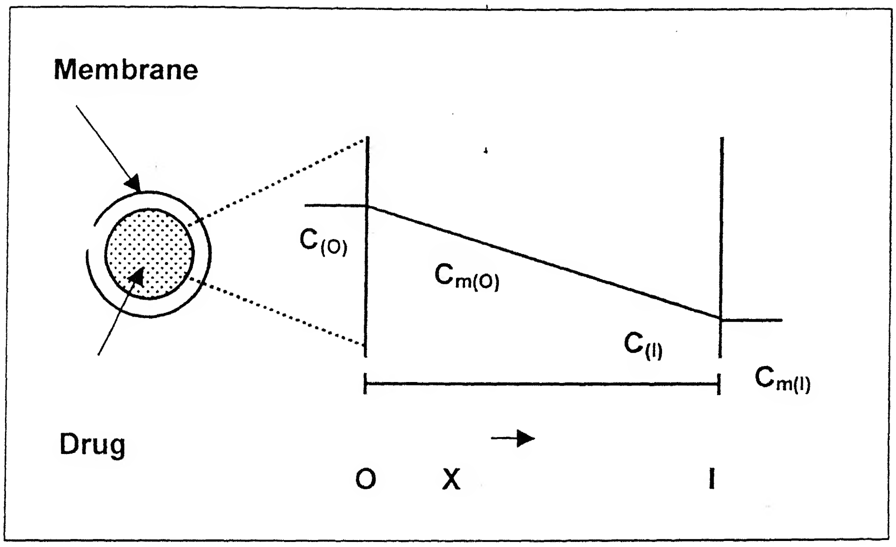


Fig. 4.5. Reservoir diffusion device representation $C_{m(o)}$ and $C_{m(l)}$ represent concentrations of drug at the inside surfaces of the membrane and $C_{(o)}$ and $C_{(l)}$ represent concentrations in the adjacent regions.

The process of diffusion is described by a series of equation described by *Fick*. Basically, there are two laws: The *Fick's* First Law and the *Fick's* Second Law of Diffusion.

Fick's First Law

The amount of drug passing across a unit area is proportional to the concentration difference across that plane. The *Fick's* First Law equation is given as

$$J = -D\,(dc/dx) \qquad (4.1)$$

where

J = flux, given in units of (amount/area) x time

D = diffusion coefficient of drug in membrane in units of area/time (dependent on molecule's ability to diffuse, its size, concentration)

dc/dx = rate of change in concentration, "*c*" with respect to the distance "*x*" in membrane.

***Fick's* Second Law**

An equation for mass transfer that emphasizes the change in concentration with time at a definite location rather than the mass diffusion across a unit area of barrier in unit time is known as *Fick's* Second Law. The *Fick's* Second Law equation is given as

$$dc/dt = D \cdot (d^2c/dx^2) \quad (4.2)$$

(in one direction)

$$dc/dt = D \cdot (d^2c/dx^2) + (d^2c/dy^2) + (d^2c/dz^2) \quad (4.3)$$

(in three directions)

The *Fick's* Second Law states that the change in concentration with time in a particular region is directly proportional to the change in the concentration gradient at that point in the system. If it is assumed that the drug on either side of the membrane is in equilibrium with the respective layer of the membrane surface can be related to the concentration in the adjacent region by the expressions

$$K = C_{mm(o)} / C_{(o)} \quad \text{at} \quad x = 0 \quad (4.4)$$

$$K = C_{mm(l)} / C_{(l)} \quad \text{at} \quad x = l \quad (4.5)$$

where K is the partition coefficient.

Assuming that D and K are constant, Eq. 4.1. can be integrated to give

$$J = DK\Delta C / l \quad (4.6)$$

where ΔC is the concentration difference across the membrane.

If the activity of the drug inside the reservoir is maintained constant and the value of K is less than unity, zero-order release can be achieved. This is the case when the drug is present as a solid, i.e., its activity is unity. Depending on the device, the equation describing drug release will vary. Only the simplest geometry that of a rectangular slab or "sandwich", presented here.

For the slab geometry, the equation describing release is

$$dM_t / dt = \quad ADK\Delta C / l \qquad (4.7)$$

where dM_t is the mass of drug released after time t, dM_t / dt is the steady state release rate time t, A is the surface of the device and D, K and l are as defined previously.

Similar equations can be written for cylindrical or spherical devices. In order to obtain a constant drug release rate, it is necessary to maintain constant area, diffusion path length, concentration and diffusion coefficient. In other words, all of the terms on the right hand side of equation 4.6 are held constant. This is often not the case in actual practice because one or more of the above terms will change in the product, thus deviation from zero order release is frequently observed.

4.6.2.A.i.b. Matrix Devices[27-39]

As the name implies, these consists of a drug dissolved or dispersed, and distributed uniformly in an inert polymeric matrix. In this model, drug in the outside layer, exposed to the bathing solution is dissolved first and then diffuses out of the matrix and continues with the interface between the bathing fluid and the solid drug moving towards the interior. Obliviously, for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must reach faster than the diffusion rate of dissolved drug leaving the matrix. The equation presented below describes the rate of release of drugs dispersed in an inert matrix system and has been derived by *Higuchi et al.*

$$Q \quad = \quad \{(D\varepsilon / \tau)\,[2A - \varepsilon C_s \,.\, t]\}^{1/2} \qquad (4.8)$$

where

Q = amount of drug released per unit surface area at time "t"

D = diffusion coefficient of the drug

t = time (hours)

ε = porosity of the matrix

τ = tortuosity of the matrix

A = total amount of drug in unit volume of the matrix

C_s = solubility of the drug in release medium

The above equation indicated that the amount of drug release is a function of square root of time.

4.6.2.A.ii. Dissolution Controlled Drug Delivery System[40-41]

Certain drugs with a slow dissolution rate will yield an inherently sustained blood levels. In principle, then it would seem possible to prepare extended release products by decreasing the dissolution rate of drugs, which are highly water-soluble. This can be done preparing an appropriate salt or derivative, by coating the drug with a slowly soluble material or by incorporating it into a tablet with a slowly soluble carrier. These products are not truly sustaining in nature, but serve as useful function in direct release of the drug to a specific site. The same approach can be employed for drugs that are degraded by the harsh conditions of the gastric region.

The Noyes-Whitney equation describes the dissolution process at steady state

$$dc/dt = K_d \cdot A\,(C_s - C) \qquad (4.9)$$

$$= D/h \cdot A\,(C_s - C) \qquad (4.10)$$

where dc/dt = dissolution rate

K_d = dissolution rate constant

D = diffusion coefficient

C_s = saturation solubility of the solid

C = concentration of solute in the bulk solution.

Types of dissolution controlled systems:

4.6.2.A.ii.a. Encapsulated Dissolution Systems

Schematic representation of encapsulated dissolution systems in given in fig.4.6 below.

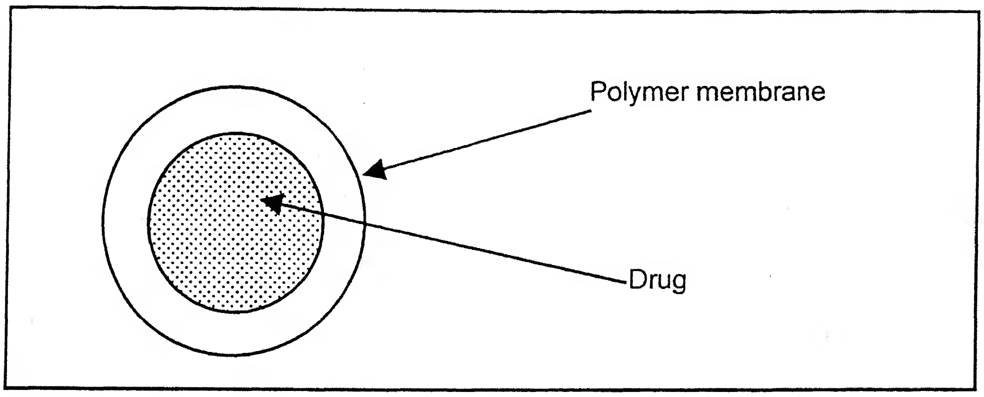


Fig. 4.6. Schematic representation of dissolution governed system.

4.6.2.A.ii.b. Matrix Dissolution Systems

Schematic representation of matrix dissolution system (fig.4.7).

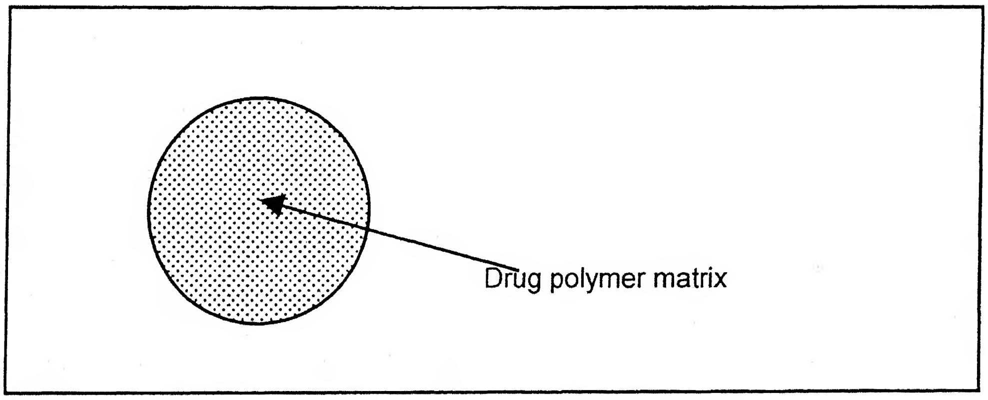


Fig. 4.7. Schematic representation of matrix dissolution governed system.

In matrix formulation, drug release is determined by dissolution rate of a polymer. Matrix dissolution systems are prepared by compressing the drug with a slowly soluble polymer carrier. Congealing method can be used for wax mixed drug or they

can also be made by direct compression of a mixture of drug, polymer and excipients.

4.6.2.A.iii. Bioerodable and Diffusion / Dissolution Combined Drug Delivery System

Practically, a therapeutic system is rarely dependent only on dissolution or only on diffusion. The dominating mechanism for release will overshadow other processes sufficiently to allow classification as either "dissolution rate limited" or "diffusion controlled". Furthermore, these systems can combine diffusion and dissolution of both the matrix material and the drug. The inherent advantage of such a system is that the bioerodible property of the matrix does not result in a "ghost matrix", which requires removal when used as an implant, while limitation is of controlling release kinetics.

Another method of preparation of bioerodible systems is to attach the drug directly to the polymer by chemical bond, the release being dependent on hydrolysis or enzymatic reaction.

A third type utilizes combination of diffusion and dissolution and involves use of swelling controlled release matrix, the system minimizing burst effect since polymer swelling must occur before drug release[41].

4.6.2.A.iv. Osmotic Pressure Activated DDS[42-43]

These systems depend on the osmotic pressure to activate the release of drug. The drug reservoir, which can be either a solution[44] or solid formulation, is contained within a semi-permeable housing with controlled water permeability. The drug is activated to release in solution form, at a constant rate through a special delivery

orifice. The rate of drug release is modulated by controlling the osmotic pressure gradient. When such a device is exposed to water or any body fluid, ingress of water into the device will ensue.

The rate of flow, (*dv/dt*) is given as

$$(dv / dt) = Ak/ h\, (\Delta l - \Delta p) \qquad (4.11)$$

where k = membrane permeability

A = area

H = thickness

Δl = osmotic pressure difference

Δp = hydrostatic pressure difference

Rate of drug release, (dm/dt) having the orifice is given by

$$(dm / dt) = (dv / dt)\, C_s \qquad (4.12)$$

where C_s is the concentration of the drug in solution.

4.6.2.A.v. Hydrodynamic Pressure Activated DDS

This type of system can be fabricated[45-46] by enclosing a collapsible, impermeable container which contains a liquid drug collapsible, to form a drug reservoir compartment inside a rigid shape retaining housing. A composite laminate of an absorbent layer and a swellable, hydrophilic polymer layer is sandwiched between the reservoir compartment and the housing.

4.6.2.A.vi. Vapor Pressure Activated DDS

In this type[47] the drug reservoir, which also exists as a solution, is contained inside the infusion compartment. It is physically pushed from the pumping compartment by a freely movable partition. The pumping compartment contains a fluorocarbon fluid

that vaporizes at body temperature from implantation site and creates a vapor pressure, which moves the partition upward, thereby forcing the drug solution to be delivered through a series of flow regulators and delivery cannulae.

4.6.2.A.vii. Mechanically Activated DDS

The drug reservoir in a solution formulation is retained in a container equipped with a mechanically activated pumping system. A measured dose is reproducibly delivered into a body cavity, through the spray head upon manual activation of drug delivery pumping system.

4.6.2.A.viii. Magnetically Activated DDS

Here, the drug reservoir is a dispersion of peptide or protein powders in a polymer matrix from which macromolecular drug can be delivered only at a relatively slow rate. This slow rate can be improved by incorporating an electromagnetically triggered vibration mechanism into the polymeric delivery device combined with a hemispherical design[48].

4.6.2.A.ix. Sonophoresis Activated DDS

This utilizes ultrasonic energy to activate the delivery of drugs from a polymeric drug delivery system.

4.6.2.A.x. Iontophoresis Activated DDS

Here, electrical current is used to activate and to modulate the diffusion of a charged drug molecule across a biological membrane, like the skin.

4.6.2.A.xi. Hydration Activated DDS

Here, the delivery upon the hydration induced swelling process to activate release of drug.

4.6.2.A.xii. pH Activated DDS

This type permits targeting the delivery of a drug only in the region with a selected pH range. It is fabricated by coating the drug-containing core with a pH sensitive polymer combination[45].

4.6.2.A.xiii. Ion Activated DDS

Such a system[45] is prepared by first complexing an ionic drug with an ion-exchange resin containing suitable counter ion, the granules of the drug-resin complex are first treated with an impregnating agent, to reduce the rate of swelling in an aqueous environment and then coated with a water-insoluble but water-permeable polymeric membrane which serves as a rate-controlling barrier to modulate the influx of ions as well as release of drug from the system.

Here, the drug bound to the resin is released by exchanging with appropriately charged ions.

$$\boldsymbol{Resin^{+} - Drug^{-} + X^{-} \longrightarrow Resin\_^{+}X^{-} + Drug^{-}}$$

This system is advantageous for drugs that at highly susceptible to degradation by enzymatic process since it offers a protective mechanism, by temporarily altering the substrate.

4.6.2.A.xiv. Hydrolysis Activated DDS

This system depends upon the hydrolysis process to activate the release of drug molecules[49].

4.6.2.A.v. Enzyme Activated DDS

The drug reservoir is either physically entrapped in microspheres or chemically bound to polymer chains from biopolymers. The release of the drug is activated by the enzymatic hydrolysis of biopolymers by the specific enzyme in target tissue[50-51].

4.6.2.B. FEEDBACK REGULATED DRUG DELIVERY SYSTEMS

In the feedback – regulated DDS, the release of drug molecules from these delivery systems is activated by a triggering agent such as biochemical substance in the body and also regulated by its concentration via some feedback mechanism. They have all the four elements of therapeutic system. These systems provides for release of a drug using controlled source of energy, which can be either physicochemical energy (like diffusion, osmosis and dissolution/ chemical reaction) or mechanical energy (by the use of elastomers and pumps and electrical or nuclear energy. These systems are further classified as:

a. Bioerosion regulated DDS
b. Bioresponsive DDS
c. Self-regulated DDS.

4.7. FACTORS INFLUENCING THE DESIGN AND PERFORMANCE OF EXTENDED RELEASE PRODUCTS

To establish criteria for the design of extended release products, a number of variables must be considered.

4.7.1. Drug Properties

The physicochemical properties of a drug, including stability, solubility, partitioning characteristics, charge, and protein binding propensity, play a dominant role in the design and performance of controlled release systems[52-53].

4.7.2. Route Of Drug Delivery

The area of the body in which drugs will be applied or administered can be restrictive on the basis of technological achievement of a suitable controlled release mechanism or device. At times, the drug delivery system, in certain routes of administration, can exert a negative influence on drug efficacy, particularly during chronic administration, and hence other routes of administration should be considered. Performance of the controlled release systems may also be influenced by physiological constraints imposed by the particular route, such as first pass metabolism, *GI* mobility, blood supply and sequestration of small foreign particles by the liver and spleen.

4.7.3 Target Site

In order to minimize unwanted side effects, it is desirable to maximize the fraction of applied dose reaching the target organ or tissue. This can be partially achieved by local administration or by the use of carriers. However, the absorptive surfaces of most routes are impermeable to macromolecules or other targeted delivery systems, thereby necessitation either intra-vascular or intra-arterial administration.

4.7.4. Acute Or Chronic Therapy

Consideration of whether one expects to achieve cure or control or a condition and the expected length of drug therapy are important factors in designing controlled release systems. Attempts to generate a one year contraceptive implant presents significantly different problems in design than does an antibiotic for acute infection. Moreover, long-term toxicity of rate-controlled drug delivery system is usually different from that of conventional dosage forms[54].

4.7.5. Disease

Pathological changes during the course of a disease can play a significant role in the design of a suitable drug delivery system. For example, in attempting to design an ocular controlled release product for an external inflammation, the time course of changes in protein content in ocular fluids and in the integrity of the ocular barriers would have to be taken into consideration. Sometimes one can take advantage of the unique manifestations of the disease state. For example, the higher plasminogen activator levels in some tumor cells can lead to preferential bioconversion of peptidyl prodrugs in these cells[55-56]. Similarly, the higher tyrosinase level in melanoma cells has been demonstrated to allow targeting to and preferential bioconversion of 2,4-dihydroxyphenylalanine in them[57].

4.7.6. Patient

Whether the patient is ambulatory or bedridden, young or old, obese or gaunt, etc., can influence the design of a controlled release product. An implant or intra-muscular injection of a drug to a bedridden patient with little muscle movement may perform in a manner significantly different from that of an ambulatory patient. Some of these factors represent individual patient variation and cannot be controlled by the scientists while others must be considered. For example, single unit controlled release products are particularly prone to intra and inter subject variation because of variability's in individual *GI* motility[58].

To establish a basis for discussion of the influence of drug properties and the route of administration on sustained/controlled release product design, it is worthwhile focusing on:

(i). Behavior of the drug in its delivery system

(ii). Behavior of the drug and its delivery system in the body.

The first of these two elements is concerned with the ways in which drug properties can influence release characteristics from its delivery system. For conventional drug delivery systems, the rate-limiting step in drug availability is usually absorption of drug across a biological membrane such as the gastrointestinal wall (Scheme 1).

$$\text{Drug (Dosage form)} \xrightarrow{\text{Drug release}} \text{Drug (Solution at absorption site)} \xrightarrow{\text{Absorption}} \text{Drug (Target area)} \xrightarrow{\text{Elimination}}$$

Scheme 1

In a sustained / controlled release product, one aims for release of drug from the dosage from as the rate limiting step instead. Thus, drug availability is controlled by kinetics of drug release rather than absorption. Consequently, the associated rate constants for drug release from the dosage form are smaller than the absorption rate constant and kinetically the process appears as shown (Scheme 2).

$$\text{Drug (Dosage form)} \xrightarrow{\text{Drug release}} \text{Drug (Target area)} \xrightarrow{\text{Elimination}}$$

Scheme 2

To control drug release one can employ variety of approaches, such as dissolution, diffusion, swelling, osmotic pressure, complexation, ion-exchange, and application of magnetic field. The interplay between physicochemical properties of a drug and characteristics of its delivery system determines the temporal release pattern that is observed.

The second element, behavior of the drug and its delivery system in the body, is extremely complex, involving the fate of drug during transit to the target area as well

The second element, behavior of the drug and its delivery system in the body, is extremely complex, involving the fate of drug during transit to the target area as well as its fate while in the bio-phase. Availability of drug to its target will depend on its pharmacokinetics as well as that of its carrier. In the case of drug targeting, the carrier is used to alter the pharmacokinetics of drug in the body. The influence of physiological constraints on the fate of the delivery system in the body is usually negative, for example, oral absorption is usually limited by *GI* transit time of the delivery system.

From the previous discussion, it is clear that the formulation and performance of sustained/controlled release dosage forms have roots in the physicochemical properties of the drug and its carrier. The pharmacokinetics and pharmacodynamics, to a large extent, are derived functions of the intrinsic properties of the drug. Thus, development and assessment of sustained / controlled drug delivery system requires a rather complete knowledge of the intrinsic properties of a drug and the ways in which it can influence the design of sustained /controlled release systems. Often times, undesirable physicochemical and biological properties can be altered by suitable chemical modifications, by use of a carrier, or perhaps by administration via another route.

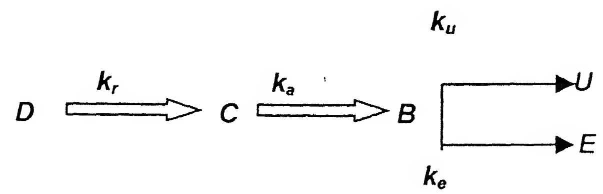
4.8. PHARMACOKINETIC MODELS FOR EXTENDED RELEASE DRUG DELIVERY SYSTEM

Objective of extended release dosage formulation is to give rapid blood concentrations of the drug sufficient to elicit the desired therapeutic effect; to maintain these concentrations at an essentially constant level for suitable period of time; to reduce the frequency of drug administration; to have more uniform biological response and reduced intensity and incidence of side effects.

To achieve these objectives, the interdependent parameters such as dosage form, drug release rate from dosage form, absorption, distribution and excretion of drug should be evaluated through a use of suitable pharmacokinetic model. These models help to formulate extended release dosage form having required blood levels with consideration also being made for calculation of initial dosage and maintenance dose.

Various pharmacokinetic models have been proposed for calculating dose and release profile of extended release dosage form. *Nelson*[59] gave a method of deriving the maintenance dose of the drug from data based on its biological half-life. *Weigand* and *Taylor*[60] presented a mathematical model and derived equation based on first order release rate of the drug from maintenance dose. *Beckett*[61] presented a model for an ideal extended release form in which there is a constant rate of release of drug from maintenance dose. They have derived kinetic equations and their implication related to the model. Limitation of this model is that between the peak time for fast release component and sustain release component, the drug level tend to be higher producing a lump in the overall blood drug level versus time profile. *Robinson* and *Eriksen*[62] have presented model, which provides analysis of kinetic relationship governing the rate of release of drugs from first order and zero order extended release dosage form. The model permit calculation of doses and of constant that will give a blood concentration versus time curve most closely approximately an idealized curves.

Following scheme 1 is used to describe *Robinson* and *Eriksen* model.



Scheme 1

where D = concentration of drug remaining in dosage form

C = concentration of drug at the site of absorption

B = concentration of drug in the fluid of distribution (blood)

U = concentration of drug in the urine

E = concentration of drug metabolized

k_r = rate constant for release of drug from the dosage from, where superscript 0 and 1 indicate the apparent order of release.

The stripped arrow is used to indicate the rate release is variable.

k_a = rate constant for absorption

k_e = rate constant for elimination via all other routes

For simplicity,

$$\boldsymbol{k_e + k_u = k_d} \qquad (4.13)$$

In this model certain assumptions are made such as one compartment model is considered. The equilibria for each lie far to the right so that the reverse reactions are negligible. The drug is completely absorbed and that after release it is immediately available. The concentration of drug at the absorption site at time zero

is initial dose (D_i) and is equal to the fraction in the initial or in the immediately available dose (F_i) times the total dose given (W). The concentration of drug at time zero as maintenance dose (D_m) is that fraction of dose (F_m) required to maintain an optimum blood level for given length of times the total dose given (W).

According to the model in case of the release of drug by zero order kinetics, blood concentration at any time is function of k_a, k_e, and concentration of drug in the gut. The concentration of drug in blood B_t, is given by following equation:

$$B_t = D_i \,.\, k_a\,(e^{-kat} - e^{-kdt}) / (k_d - k_a) \qquad (4.14)$$

The time required 'Tp' to achieve peak concentration is given by

$$T_p = 2.3\,[\log (k_a/k_d)] / (k_a - k_d) \qquad (4.15)$$

Total dose $W = D_i + D_m$ (4.16)

where 'D_i' is initial dose and 'D_m' is maintenance dose.

The maintenance dose 'D_m' and time over which extended action (h) is desired is

$$D_m = k_r^0 \times h \qquad (4.17)$$

k_r^0 can be roughly estimated as

$$k_r^0 = k_d \times B_d \qquad (4.18)$$

where 'B_d' is desired blood level.

The initial dose is given as

$$D_r = D_b - (k_r^0 \, X \, T_p) \qquad (4.19)$$

where 'D_b' is immediate dose to produce peak equal to desired blood level.

According to the model in case of the release of drug by first order kinetics, blood concentration at any time 't' is function of 'K_a', 'K_e' and concentration of drug in the gut. The concentration of drug in blood 'Bt', is given by following equation:

$$B_t = D_m k_a k_r' (e^{-kr't} - e^{-kdt}) / (k_d - k_r') + [D_i K_a - (D_m k_a k_r' / k_a - k_r')]. (e^{-kat} - e^{-kdt}) / (k_d - k_r') \quad (4.20)$$

Total dose (W) can be calculated as follows:

$$W = D_i + D_m \quad (4.21)$$

where $D_i = D_b - D_{(correction)}$

$$D_{(correction)} = D_m (k_r' T_p) \quad (4.22)$$

Therefore,

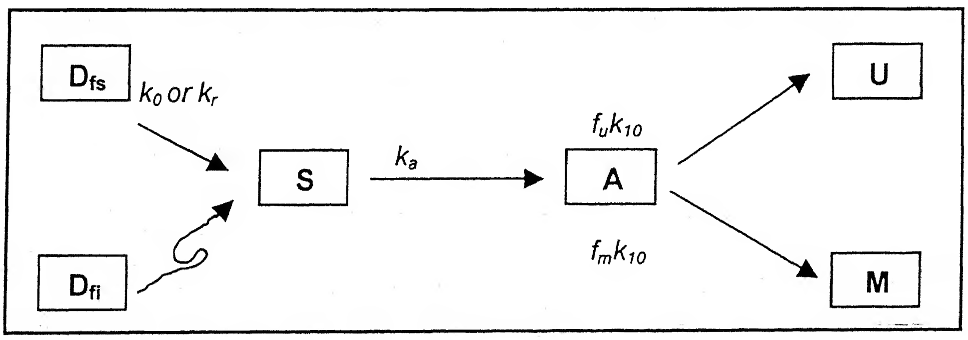
$$D_i = (D_b - D_m) k_r' T_p \quad (4.23)$$

$$D_m = (k_d - B_d) / [k_r' - (K_r')^2 t] \approx K_d B_d / k_r' \quad (4.24)$$

Using above equation:

$$W = D_b - D_m k_r' T_p + (K_d B_d / k_r') \quad (4.25)$$

Dobrinska and *Welling*[63-64] have proposed model, which describes the pharmacokinetic behavior of extended release dosage forms. The schematic representation of the model is –



where

D_{fi} = dose instantaneously available for absorption into the systemic circulation,

D_{fs} = maintenance dose to be released slowly at the absorption site,

S = total drug in solution and available for absorption from the absorption site,

A = amount of unchanged drug in the body,

U = cumulative amount of drug excreted unchanged in the urine,

M = cumulative amount of drug converted to metabolites or excreted by any process other than via the kidneys, i.e., in bile, sweat, saliva, etc. For brevity, this will be referred to in the text as metabolites,

k_0 = zero order rate constant for release of drug from D_{fs},

k_r = first order rate constant for release of drug from D_{fs},

k_{10} = first order rate constant for transfer of drug from the absorption site into the systemic circulation,

$f_u k_{10}$ = first order rate constant for excretion of unchanged drug into urine

$f_m k_{10}$ = first order rate constant for drug metabolism and all other routes of extra renal excretion (see 'M' above)

k_{10} = first order rate constant for overall elimination of drug from the body (= $f_u k_{10} + f_m k_{10}$)

The curved arrow represents instantaneous release of drug from the dosage form to the absorption site. The simplifying assumptions embodied for the model are

(i) Absorption, metabolism and excretion are all first order processes;

(ii) Transfer from one compartment to another is irreversible;

(iii) All the drug which is released into the gastrointestinal tract or any other absorption site in the body is completely absorbed as intact drug;

(iv) Release of drug from the extended release portion is the rate-limiting step in the absorption process, and

(v) Drug distributes into one apparently homogeneous distribution volume in the body after absorption, i.e., simple-one compartment kinetics are operative.

Assumption (v) is reasonable on the basis that, for a drug obeying multi-compartment kinetics within the body, it would be difficult to define the microscopic distribution parameters when drug is introduced into the system at a slow rate. Even when a fast-release component is included in a drug formulation, the simple one compartment model is a reasonable compromise between pharmacokinetic accuracy, with accompanying mathematical complexity and practical utility.

4.8.1. CASE 1: Zero Order Drug Release From Dosage Form With No Instantaneous Release Component

In such system $D_{fi} = 0$ and $D_{fs} = k_0T$

where T is the total time during which drug is release.

Drug release $D^t_{fs} = D_{fs} - k_0\, t$ (4.26)

The above equation describes the quantity of drug in the formulation remaining to be released at any time t after dosing; where t varies form zero to T.

Drug at absorption site is given by the equation

$$S = k_0\,(1 - e^{-kat})\,k_a \qquad (0 \leq t \leq T) \qquad (4.27)$$

The above equation describes the time cause of amount of drug in solution at the absorption site.

Drug in the body is given by

$$A = k_0\,(1 - e^{-k_{10}t})\,k_{10} \qquad (4.28)$$

4.8.2. CASE 2: ZERO ORDER DRUG RELEASE FROM DOSAGE FORM WITH INSTANTANEOUS RELEASE COMPONENT

In this model D_{fi} is available f - instantaneous absorption.

Drug release is given by equation:

$$D^t_{fs} = D_{fi} - k_0\, t \qquad (4.29)$$

Integration of above equation givens

$$D^t_{fs} = D_{fi} - e^{kat} \qquad (4.30)$$

This equation describes mono exponential loss of the instantaneously available component from the absorption site, controlled by k_a.

Drug at the absorption site at any time $t \leq T$ is given by

$$S = k_0\,(1 - e^{-kat}) / k_a + D_{fi}\, e^{-kat} \qquad (4.31)$$

Drug in the body at any time $t \leq T$ is given by

$$A = k_0\,(1 - e^{-k}{}_{10}{}^{t}) / k_{10} + [(k_a D_{fi} - k_0)\,(e^{-kat} - e\text{-}{}^{k}{}_{10}{}^{t})] \div (k_{10} - k_a) \qquad (4.32)$$

D_{fs} can be calculated from

$$D_{fs} = [1/k_a - (k_{10} - k_a)\,(1 - e^{-k}{}_{10}{}^{t}) / k_{10}k_a\,(e^{-kat} - e\text{-}{}^{k}{}_{10}{}^{t})]\, k_0 + A\,(k_{10} - k_a) / k_a\,(e^{-kat} - e^{-k}{}_{10}{}^{t}) \qquad (4.33)$$

Simplified form of above equation

$$D_{fs} = k_0 / k_{10} \qquad (4.34)$$

4.8.3. CASE 3: First Order Drug Release From Dosage Form With No Instantaneous Release Component

For first order release model, with not instantaneous release ($D_{fi} = 0$) drug release is given by the following equation:

$$D^{t}_{fs} = D_{fs}\, e^{-krt} \qquad (4.35)$$

Drug at absorption site

$$S = D_{fs}\, k_r\, (e^{-krt} - e^{-kat}) / (k_a - k_r) \qquad (4.36)$$

Drug in the body is given as

$$A = D_{fs}\, k_r\, (e^{-k_{10}t} - e^{-krt}) / (k_r - k_{10}) \qquad (4.37)$$

Drug in the body A is given by

$$A = D_{fs}\, k_a\, k_r\, \{e^{-kat} / k_{10} - k_a)(k_r - k_a) + e^{-krt} / (k_a - k_r)(k_{10} - k_r)$$
$$+ e^{-k_{10}t} / (k_r - k_{10})\,(k_a - k_{10})\} \qquad (4.38)$$

4.8.4. CASE 4: First Order Drug Release From Dosage Form With Instantaneous Release Component

For first order release model, with instantaneous release, drug release is given by the following equation:

$$D^{t}_{fs} = D_{fs}\, e^{-krt} \qquad (4.39)$$

Drug at absorption site

$$S = D_{fi}\, e^{-kat} + D_{fs}\, k_r\, (e^{-krt} - e^{-kat}) / (k_a - k_r) \qquad (4.40)$$

Drug in the body A is given by

$$A = D_{fs}\, k_a\, k_r\, \{(k_a - k_{10})\, e^{-krt} + (k_{10} - k_r)\, e^{-kat} + (k_r - k_a)$$
$$e^{-k_{10}t}\} \div (k_r - k_a)\,(k_r - k_{10})\,(k_a - k_{10}) \qquad (4.41)$$

Total dose D for this case contain loading dose D_{fi} required to reach the desired therapeutic level at its peak, minus the drug simultaneously released from D_{fs} up to time t_{max} plus the D_{fs} required to maintain the level.

$D_{fi} = D_c' - D_{corr}$

D_c' = initial dose to reach desired peak level.

D_{corr} is correction factor allowing for the contribution due to D_{fs} to time t_{max}.

Total dose $D = D_c' - D_{fs} - D_{fs}\, k_r\, t_{max} + [k_{10}\, A_{(ss)} / k_r]$ (4.42)

4.9. ORAL EXTENDED RELEASE DRUG DELIVERY SYSTEM – PHYSCIO-CHEMICAL AND PHYSOLOGICAL ASPECTS

Among all the routes of drug administration that have been explored for the development of extended release delivery system, the oral route has by far achieved the most attention and success. This is due, in part to the ease of administration as well as the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes.

An understanding of varied disciplines, such as *GI* physiology, pharmacokinetics, and formulation techniques, is essential in order to achieve a systematic approach to the design of oral ER products. The scientific framework required for development of a successful oral extended drug delivery dosage form consists of an understanding of two aspects of the system, namely

- Formulation characteristics
    - Physicochemical characteristics of the drug.
    - Dosage form characteristics.
- *GI* anatomical and physiological features.

4.9.A. FORMULATION CHARACTERISTICS

A number of formulation characteristics need to be considered in evaluating drug candidate, polymers and excipients for oral ER dosage forms. Some of these characteristics are discussed here.

4.9.A.i. Dose

A total dose of several grams may be administered orally as single or multiple units to obtain and maintain adequate drug levels. Nevertheless, for drug with elimination

half-life or less than 2 hour as well as those that are administered in large doses in CR dosage form may need to carry a prohibitively large quantity of drug.

4.9.A.ii. Biological Half Life[39]

In general, drug with short half-lives (2-4 hours) make good candidate for ER systems.

Drugs with elimination half-lives of over 8 hours are commonly sufficiently extended in the body after a conventional oral dose to make extended release unnecessary.

4.9.A.iii. Therapeutic Range

Oral ER formulations are valuable for maintaining plasma levels within a narrow therapeutic range. In fact, a valid rationale for formulating drugs with half-lives of over 8 hours as ER formulations is to maintain plasma drug levels with a narrow range.

4.9.A.iv. *GI* Absorption[65-72]

Efficient drug absorption from the *GI* tract is a perquisite for a drug to be considered for use in an oral ER form. In general, the absorption rate for most drugs decreases as the dosage form moves beyond the jejunum. As long as the absorption rate remains above that of the release rate, this change does not affect plasma levels. However, once pas the ileocecal junction, a variety of factors generally reduce the drug absorption rate to below acceptable values. This creates a time limit of about 6-9 hour during which the drug can be delivered in a predictable manner. For compounds that are absorbed via an active transport mechanism and for many others, an acceptable rate of absorption may exist only from a limited portion of the small intestine, which may further limit their suitability for ER systems.

4.9.A.v. Ionization, pK_a And Aueous Solubility

Most drugs are weak acids or bases. Since the unchanged form of a drug preferentially permeates across lipid membranes, it is important to note the relationship between the pK_a of the compound and the absorptive environment. Considering that these dosage forms must function in an environment of changing pH, the stomach being acidic and the small intestine more neutral, the effect of pH on the release processes must be defined.

Compounds with very low solubility (less than 0.01 mg/ml) are inherently extended, since their release over the time course of a dosage form in the *GI* tract will be limited by dissolution of the drug. ER formulations of low solubility drugs may be aimed at making their dissolution more uniform rather than reducing it[73-77].

4.9.A.vi. Stability Of Wide pH Range *GI* Enzymes And Flora

Typically the drug must be stable in the pH range of 1 to 8. Unlike a conventional dosage form, an ER formulation is exposed to the entire range of *GI* pH, enzymes and flora.

4.9.A.vii. First-pass Metabolism[78-79]

Saturable hepatic metabolism may render a drug unsuitable for oral CR. This is because systemic availability for such drugs is highly reduced when the input rate is small.

4.9.A.viii. ER Polymer Properties[80-95]

Understanding polymer properties is must, since in most of the extended release system drug release mechanism are based on diffusion through polymer, erosion of polymers and other characteristics such as osmotic and ion exchange properties.

The polymer properties that influence drug release are:

(i). Molecular weight and molecular weight distribution.

(ii). Material characteristic time.

(iii). Polymer microstructure.

(iv). Glass transition temperature.

(v). Solubility parameter.

(vi). Diffusibility.

The details are in Chapter 5.

4.9.B. EFFECT OF DOSAGE FROM SHAPE ON DRUG RELEASE

The release of drug from planar device was first proposed by Higuchi[79] who used a pseudo steady state approximation approach to simplify complex boundary problem and is illustrated in fig. 4.8.

$$Q_t = AD_m\, dc/dx \qquad (4.43)$$

where Q_t = rate of diffusion

A = cross section area available for diffusion

D_m = diffusion coefficient

c = concentration of drug

x = distance measure from the solvent matrix interface.

4.9.B.i. Slab Geometry

Consider following boundary condition

$C = C_b\, K$ at $x = 0$ and

$C = C_b$ at $x = 0\; X_{(t)}$

where

C_b = drug concentration in the bulk, which is constant over the period of release

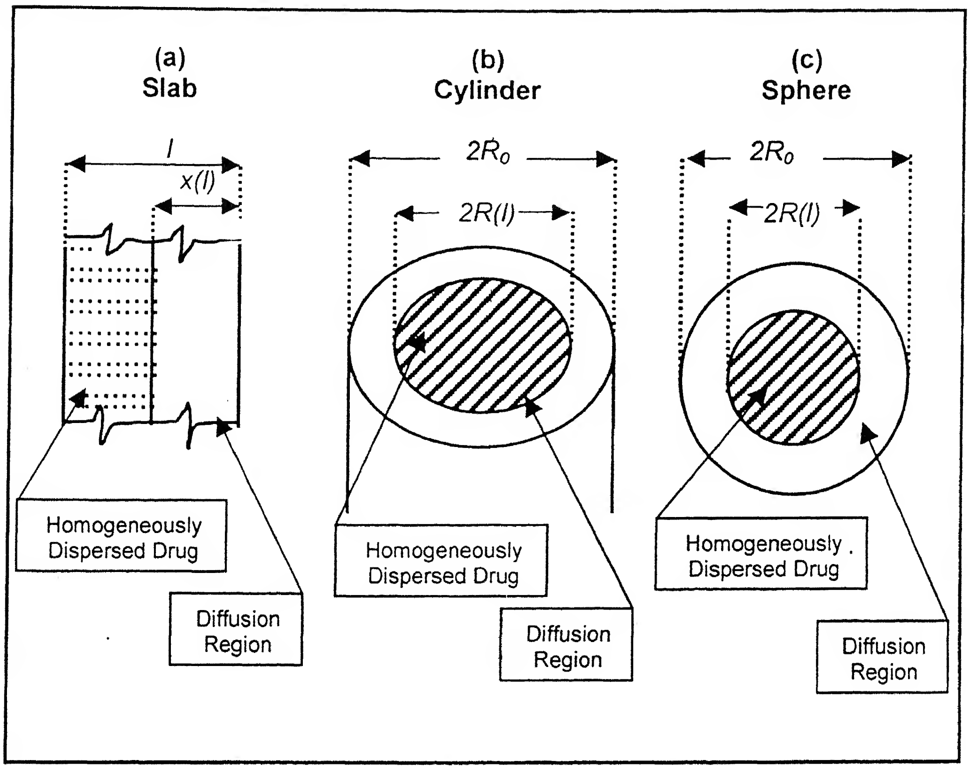


Fig. 4.8. Co-ordinate system to study drug release kinetics from plannar cylindrical and spherical geometry.

C_m = drug solubility in the matrix

K = matrix to bulk partition coefficient

$x\ (l)$ = receding boundary length is function of time

On application of above condition, integrating the equation, applying mass balance equation in diffusion region gives following equation:

$$\boldsymbol{dM_t/dt = Q_t = A\,.\,[D_m\,(C_m - C_bK)\ 2C_T - C_m - C_bK) \div 4t]^{1/2}} \quad (4.44)$$

where

M_t = amount of drug released at time t

C_T = drug loading dose in matrix.

It can be clearly seen from above equation that the release rate in slab is inversely proportional to square root of time.

Cumulative drug release and receding boundary length is directly proportional to square root of time.

4.9.B.ii. Cylindrical Geometry

For cylindrical geometry (fig. 4.8), Qt = rate of diffusion is given by the equation

$$Q_t = 2\pi r L D_m. (dc/dr) \qquad (4.45)$$

Consider following boundary condition:

$C = C_b K$ at $r = R_0$

$C = C_m K$ at $r = R_{(t)}$

Integrating above equation and making appropriate mass balance equation gives following implicit equation

$$dM_t/dt = Q_t$$

$$= 2\pi L D_m. (C_m - C_bK) \div \ln [R_0/Rct]^{1/2} \qquad (4.46)$$

$$[R^2(t)/ 2. C_n . R(t)/R_0] + 1/4 [R_0^2 - R^2 (t)] = D_m (C_m - C_bK)t / C_T$$

(4.47)

4.9.B.iii. Spherical Geometry

For spherical device (fig. 4.8), Qt = rate of diffusion is given by the equation

$$Q_t = - 4\pi r^2 D_m. (dc/dr) \qquad (4.48)$$

at $C = C_b K$ at $r = R_0$

$C = C_m K$ at $r = R_{(t)}$

$$Q_t = - [4\pi D_m. (C_m - C_bK)] \div (1/R (t) - (1/R_0) \qquad (4.49)$$

Thus, like cylindrical geometry, spherical geometry shows concentration profile for pseudo state assumption is no longer linear with radius. The rates and fraction for three geometrics when plotted against time t does not give zero order release. The release behavior is inherently first order in nature which is due to increase in

diffusional resistance and decrease in effective area at diffusional front as drug release proceeds. Methods of altering kinetics of drug release from the inherent first order behavior, to achieve constant rate of drug release from matrix device have involved use of geometry factor, erosion/dissolution, swelling control, uniform drug loading and matrix membrane combination.

4.9.C. DRUG RELEASE FROM SWELLING CONTROLLED SYSTEMS

It is reviewed in detail in Chapter 5.

4.9.D. GENERAL POLYMER TOXICOLOGICAL CONSIDERATIONS

The potential adverse effects of polymers must be known or evaluated prior to using in drug delivery system for humans. Potential adverse effects may result from contact with the polymer or from leachables such as residual monomers, reactive agents, or processing additives. The effects of polymers or extracts will be dependent on unique chemical characteristic and the amount (or dose) of polymer /extract administered. There should be an evaluation of whether the polymer is in direct or indirect contact with the drug-containing component of the system or with tissues of the patient. These evaluations will assist in the determination of the types of safety assessments that may be required during the various stages of the development process. To assist in selection of materials, a review of the manufacture's and published scientific literature should be conducted to gather clinical and non-clinical safety information. If necessary, *in vivo* and *in vitro* tests are used to evaluate the incompatibility of the polymer and/or extract acid of the drug delivery system, thereby ensuring the safety of the system. *In vitro* studies should be conducted prior to initiating *in vivo* studies. Cytotoxicity tests are simple and rapid *in vitro* procedures that can provide predictive information on *in vivo* biocompatibility of polymeric materials[96]. If polymer is not absorbed or data indicate that blood levels

are acceptable based on historical exposure or existing toxicological data, then it may be sufficient to conduct toxicological studies with the final drug delivery formulation with a written review and justification of the use of the polymer.

If the polymer is an NCE (new chemical entity), a series of *in vitro* and *in vivo* (animal) genotoxicity studies should be conducted. These mutagenecity and clastogenicity studies determine if the plolymer harms the cell's DNA. If the assays reveal a genotoxic result in multiple assays, development of the polymer should be halted. If no genotoxic activityis present, the next step is to quantify exposure. If the polymer is absorbed from the *GI* tract, a full toxicology program consisting of acute, chronic, reproduction and carcinogenicity testing is likely to be required. If the polymer is not absorbed, studies up to 6 months may be required with an evaluation of any proliferative changes. If proliferative changes occur, a carcinogenicity study might be indicated. Whether or not the polymer is absorbed or not, additional toxicology studies need to be conducted with the final formulation at multiple doses.

4.9.E. *GASTRO INTESTINAL* ANATOMY AND PHYSIOLOGY

Insight into the biological aspects of oral delivery is more important for CR systems than it is for conventional dosage forms. Listed below are some of the factors that influence delivery of drugs to the *GI* tract. *GI* mobility and transit time, blood flow, environment of *GI* tract which includes luminal contents and pH, mucus, ileo-cecal junction, gut flora, gut immunology.

4.9.E.I. *GI* Anatomy

Fig. 4.9. is the schematic representation of the route of oral drug delivery and Table 4.1 lists some of the characteristics of *GI* tract that are relevant to drug delivery system.

4.9.E.ii. *Gastro Intestinal* Motility

An important consideration when contemplating use of CR dosage forms in the *GI* tract is the continuous motility of this organ. The pattern and force of the motility vary depending on whether the animal is in a fed or a fasted state[97-98]. It is now well documented that there are two modes of *GI* motility patterns in humans and animals

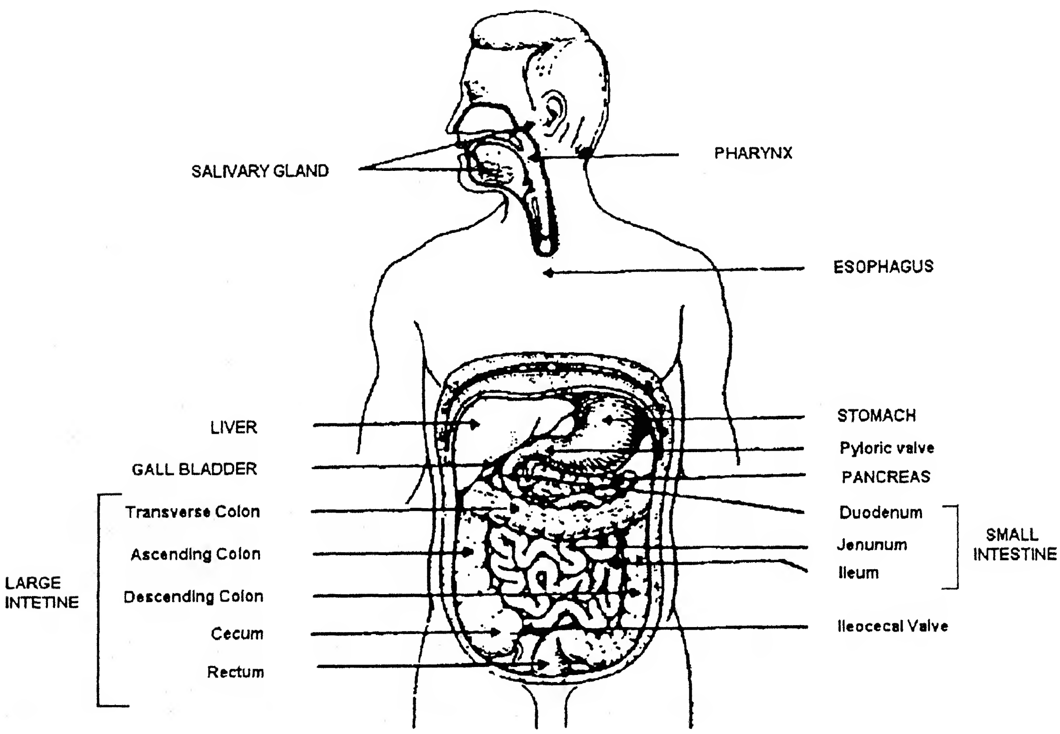


Fig. 4.9. Schematic representation of gastrointestinal tract.

Table 4.1. Characteristics of the *GI* tract.

Section	Area (m^2)	Fluid secretion (l/d)	Reaction (pH)	Important Constituents	Food Transit Time (hr)
Oral cavity	~ 0.05	0.5 –2	5.2 – 6.8	Amylase, Ptyalin, Mucins	Short
Esophagus	-	-	-	-	Very short
Stomach	0.1 – 0.2	2 - 4	1.2 – 3.5	Lipase, Cathepsin, HCl, Pepsin, Lipase, Intrinsic Factor	0.25– 3
Duodenum	~ 0.04	1 – 2	4.6 – 6.0	Amylase, Lipase, Bile acids, Glucohydrolase, Galactohydrolase, Trypsin, Chymotrypsin	1 – 2
Small Intestine	4500[a]	0.2	4.7 – 6.5	Like in duodenum	1 - 10
Large Intestine	0.5 -1	About 0.2	7.5 – 8.0	Mucus, Bacteriums	4 - 20

[a] Taking intestinal microvilli area into account; without them, ~ $100m^2$.

that consume food on a discrete basis; the digestive (fed) mode and the inter-digestive (fasted) mode[99]. Under fasting conditions both motor and secretory activities of the stomach, gut, pancreas and liver change periodically to provide both mathematical and chemical means of intestinal characteristics in a cyclic manner, each of 90–120 min[70]. A normal meal changes the motility pattern to a fed state for up to 8 hr depending on caloric content of the food[71-72].

4.9.E.ii.a. *GI* Transit

The single most limiting biological factor in the development of once daily oral ER systems is the transit time of a dosage form through the *GI* tract.

4.9.E.ii.b. Fasted State Transit Behavior

The process of disintegration and dissolution starts in the stomach. Transit of liquids already present in the stomach and administered with the dosage form can play an important role in the process. A dosage form given with a small volume of liquid can stay in contact with that liquid in the fasted state up to 60 min[70]. A solid dosage form stay in a fasted stomach for any duration up to 120 min[79]. Thus, manipulation of density and shape of solids does not seem to be a viable approach, although some studies have claimed otherwise. The only possibility may be to increase the size of the dosage form to a degree that it cannot pass through the pylorus until degraded or perhaps convert the stomach to a fed state.

For multiunit dosage forms, once the particles have left the stomach, there is, if any further spreading of particles in the intestine. Since particles usually leave the stomach as a bolus during the fasted state, multiunit dosage forms may not serve their intended claim of dispersion[100].

4.9.E.ii.c. Fed State Transit Behavior

In general, solids are not empties in the fed state unless they have been ground to a particle size of 2mm or less. Multiunit dosage forms however will disperse and empty with food and thus achieve a better degree of distribution than tablets. Total time for gastric emptying varies from about 2 to 6 hr.

4.9.E.ii.d. Effect Of Food On Drug Administration

The presence of food in the *GI* tract can often have a marked and sometimes variable effect on drug absorption. Food can increase or decrease the rate or extent of absorption of a drug, or delay the onset of absorption[100-102].

In general, food prolongs the gastric residence time of non-digestible. solids for up to 6 hour. For formulations designed to release drug independent of pH, gastric residence time does not affect drug release and subsequent absorption, unless the drug is unstable in an acid environment. For such formulations, food generally improves the bioavailability. Food can have a marked influence on the *GI* distribution of multiunit dosage forms provided they are 2 mm or smaller[65,101].

4.10. ORAL EXTENDED RELEASE DRUG DELIVERY SYSTEMS: FORMULATION ASPECTS[103-111]

The thrust of oral extended release efforts has been focused mostly on the dosage forms with 'well-defined' CR profiles. Almost all the oral solid ER products in today's market are based on the designs of matrix, membrane controlled, and osmotic systems (Table 4.2). The mechanisms of these CR dosage forms generally involve drug diffusion through a viscous gel layer, tortuous channels or a barrier, drug dissolution via system erosion: and drug solution or suspension forces out of the device by osmotic pressure. In this section, the more common methods that used to achieve extended release of orally administered drugs are discussed[112].

Table 4.2. Common oral extended release polymeric systems feasible for commercial development.

Matrix Systems	Reservoir Systems	Osmotic Systems
Hydrophilic matrix: • Swellable. • Swellable & erodible.	Coated beads or tablets. Microencapsulation	Elementary osmotic pump. Push-pull system. Push-layer system.
Hydrophobic matrix: • Homogeneous (non porous) • Heterogeneous (porous) 1. Inert (monolithic) 2. Erodible 3. Degradable		Push-stick system.

4.10.1. Matrix Controlled Drug Delivery System

The three major types of materials used in the preparation of matrix devices are insoluble plastics, hydrophilic polymers and fatty compounds. Plastic matrices include methyl acrylate-methyl methacrylate, polyvinyl chloride and polyethylene. Hydrophilic polymers include methylcellulose, hydroxypropyl methylcellulose, sodium carboxymethylcellulose and carbopol. Fatty compounds include various waxes such as carnauba wax and glyceryl tristearate.

The most common method of preparation is to mix the drug with the matrix material and then compress the mixture into tablets. In the case of wax matrices, the drug is generally dispersed in molten wax, which is then congealed, granulated and compressed into cores. In any extended release system, it is desirable to release a portion of drug immediately as a priming dose, and the remainder to be release in an extended fashion. This can be accomplished in a matrix tablet by placing the priming dose in a coat of the tablet. The coat can be applied by press coating or by conventional pan or air suspension coating. Table 4.3 gives some matrix diffusion controlled products.

Table 4.3. Matrix diffusion controlled products.

Product	**Active Ingredient(s)**	**Manufacturer**
Fero-Gradumet	Ferrous Sulphate	Abbott
Desoxyn	Methamphetamine HCl	Abbott
Procan SR Tablets	Procainamide	Parke-Davis

Matrix dissolution devices are prepared by compressing the drug with a slowly soluble polymer carrier into a tablet. There are two general methods of preparing drug-matrix particles: congealing and aqueous dispersion methods. In the congealing method, drug is mixed with a wax material and either spray congealed or congealed and screened. In the aqueous dispersion method, the drug wax mixture simply is sprayed or agitated in water and the resulting particles are collected. Matrix tablets also are made by direct compression of a mixture of drug, polymer and excipients. Some marketed preparations are mentioned in Table 4.4.

Table 4.4. Matrix dissolution products.

Product	Active Ingredient(s)	Manufacturer
Dimetane	Brompheniramine	Robins
Mestinon	Prridostigmine bromide	Roche
Nicobid	Nicotinic acid	Rhone-Poulenc Rorer
Demazin	Chlorpheniramine maleate phenylephrine HCl	Schering

4.10.2. Reservoir Controlled Drug Delivery System

In developing reservoir polymeric systems, commonly used methods include micro-encapsulation of drug particles, coating of tablets or multi-particulates, and press coating of tablets. A polymeric membrane offers a predetermined resistance to drug diffusion from the reservoir to the sink. The driving force of such systems is the concentration gradient of active molecules between reservoir and sink. The resistance provided by the membrane is a function of film thickness and characteristics of both the film and the migrating species in a given environment. The mechanisms of the drug release from the film-coated dosage forms may be categorized into (a) transport of the drug through a network of capillaries filled with dissolution media; (b) transport of the drug through the homogeneous film barrier by

diffusion; (c) transport of the drug through a hydrated swollen film; and (d) transport of the drug through flaws, cracks and imperfections within the coating matrix.

Some materials used as the membrane barrier coat, alone or in combination, are hardened gelatin, methyl or ethylcellulose, polyhydroxymethacrylate, hydroxypropylcellulose, polyvinylacetate, various waxes and silicone elastomers. Some reservoir diffusion controlled products available in the market are given in Table 4.5.

Table 4.5. Matrix reservoir controlled products.

Product	Active Ingredient(s)	Manufacturer
Nico-400 Capsules	Nicotinic acid	Jones
Nitro-Bid	Nitroglycerin	Marion
Cerespan	Papaverine HCl	Rhone Poulenc Rorer
Bronkodyl SR Capsules	Theophylline	Sanofi - Winthrop

Encapsulated dissolution systems can be prepared either by coating particles or granules of drug with varying thickness of slowly soluble polymers or by micro-encapsulation. Microencapsulating can be accomplished by suing phase separation, interfacial polymerization, heat-fusion or the solvent evaporation method. The coating materials may be selected from a wide variety of natural and synthetic polymers, depending on the drug to be coated and the release characteristics desired. The most commonly used coating materials include gelatin, carnauba wax, shellac, ethycellulose, celluloseacetate phthalate or cellulose acetate butyrate. Drug release from micro-capsules, is a mass transport phenomenon; can be controlled by adjusting the size of microcapsules, thickness or coating materials and the diffusivity of core materials. The coating thickness of microcapsules is normally very less, and

for a given coat-core ratio, it decreases rapidly as the microcapsule size decreases. The thickness can be varied from less than 1 μm to 200 μm by changing the amount of coating material from 3 to 30% of the total weight. If only a few different thicknesses is used, usually three or four, drugs will be released at different, predetermined times to give a delayed release effect, i.e., repeat action. If a spectrum of different thickness is employed, a more uniform blood level of the drug can be obtained. Microcapsules commonly are filled into capsules and rarely are tabletted as their coatings tend to disrupt during compression. Some marketed preparations are mentioned in Table 4.6.

Table 4.6. Encapsulated dissolution products.

Product	**Active Ingredient(s)**	**Manufacturer**
Dexedrine Capsules	Dextro amphetamine	Smithkline Beechem
Thorazine	Chlorpromazine HCl	Smithkline Beechem
Diamox	Acetazolamide	Lederle
Ferro-sequels	Ferrous fumarate docusate sodium	Lederle

4.10.3. Osmotic Controlled Drug Delivery System

Osmotic pressure can be employed as the driving force to generate a constant release of drug provided a constant osmotic pressure is maintained and few other features of the physical system are constrained. Consider a tablet consisting of a core of an osmotically active drug, or core of an osmotically inactive drug, in combination with an osmotically active salt surrounded by a semi-permeable membrane containing a small orifice. The membrane will allow free diffusion of water, but not drug. When the tablet is exposed to water or any fluid in the body, water will flow into the tablet due to osmotic pressure difference.

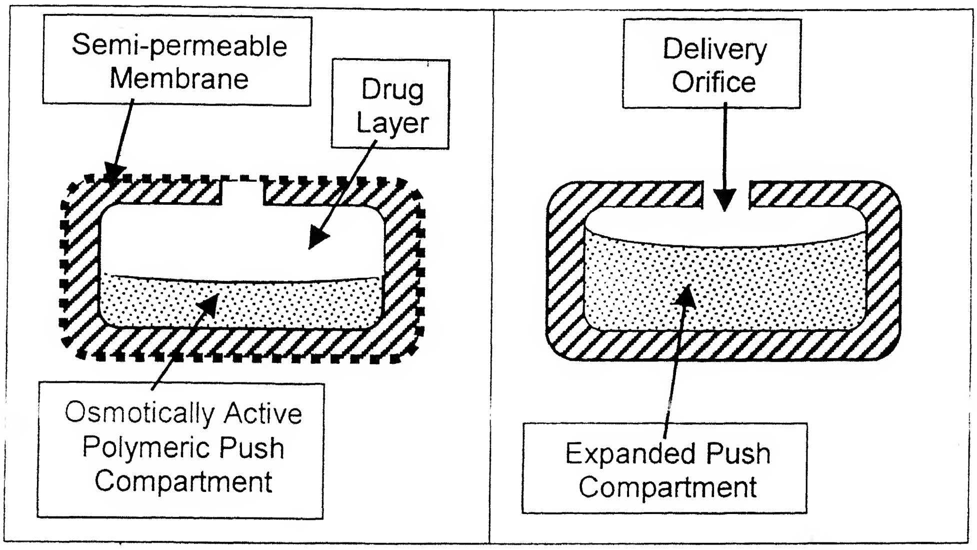


Fig. 4.10. Schematic representation of a two-compartment osmotic pressure controlled drug delivery system.

Several modifications of the osmotic pressure controlled drug delivery system have been developed. A layer of bio-erodible polymer can be applied to the external surface of the semi-permeable membrane. A system consists of two compartments separated by a movable portion (fig. 4.10). For a system that does not have an orifice, pressure is built up until the wall ruptures and the contents are released to the environment.

The advantage of the osmotic system is that it requires only osmotic pressure to be effective and is essentially independent of the environment. The drug release rate can be predetermined precisely regardless of pH change through the *GI* tract. Some materials used as the semi-permeable membrane include polyvinyl alcohol, polyurethane, cellulose acetate, ethylcellulose and polyvinyl chloride. Drugs that have demonstrated successful release rates are potassium chloride and acetazolamide.

4.10.4. Controlled Drug Delivery System Using Ion-Exchange Resins

Ion-exchange resins are water-insoluble cross-linked polymers generally as powders or beads, containing salt forming groups in repeat positions on the polymer chain. Drug is bound to the resin by exposure of the resin to the drug in a column, or by contact of the resin with the drug solution. The drug resin then is washed to remove free, unbounded and contaminating ions and dried to form particles or beads. Drug release from the drug resin complex depends on the ionic environment, i.e., pH and electrolyte concentration within the *GI* tract as well as properties of the resin.

Drug molecules attached to the resin are released by exchanging with appropriately charged ions in the *GI* tract followed by diffusion of the free drug molecule out of the resin. The rate of diffusion is controlled by the area of diffusion, diffusional path-lengths and extend of cross-linking in the resin. A modification of the release rate can be made, by coating the drug with resin complex. Further improvement of this ion exchange type drug delivery system is called the Penn Kinetic system. In this system, the drug containing resin granules first treated with an impregnating polymer such as PEG 4000 to retard the rate of swelling in water and further coated with water insoluble polymer such as ethylcellulose, to serve as a rate limiting barrier to control the drug release.

Most ion exchange resins employed in extended release products contain sulfonic acid groups that exchange cationic drugs such as those with an amine functionality. Examples of some of these drugs are amphetamine, phenyl butylamine (phenetermine), phenyltoloxamine and hydrocodone.

4.10.5. *Gastro* Retentive Drug Delivery System

Variability in *GI* transit time is a concern for oral controlled drug delivery systems[113]. Drugs with a narrow absorption window in the *GI* tract are particularly susceptive to variation in both availability and times to achieve peak plasma levels. In successful, gastro retentive controlled release formulations could offer a potential solution to the problem by offering a prolonged gastric residence time[114]. A drug that is released from the dosage form in a controlled manner in the stomach will exit the stomach together with gastric fluids and have the whole surface area of the small intestine available for absorption. This type of drug delivery also offers a potential for enhanced drug therapy for local conditions affecting the stomach. For example: antibiotic administration for Haemophilus pylori eradication in the treatment of peptic ulcer.

Researchers in the area have attempted to achieve prolonged gastric retention by several means, including altering the density of the formulations and bio-adhesion in the stomach lining. Several strategies have been employed to make the dosage forms float in the stomach. Hydro-dynamically balanced system (HBS) was the first formulation that uses the floating property of a device with density lower than water[115]. HBS is a capsule-containing drug, gel-forming hydrophilic polymers (e.g., hydroxypropylcellulose), and some hydrophobic fatty materials (e.g. stearates)[116]. In a different approach for gastric retention, ion exchange resin beads are loaded with bicarbonate, which, on contact with media containing hydrochloric acid, release carbon dioxide, causing the resin to float[117]. Extension of the floating time is achieved by coating the bicarbonate-coated beads with a semi-permeable membrane. Recently, a multiple-unit floating dosage form has been prepared from freeze-dried calcium alginate. In fed subjects, these floating units were retained in the stomach for 8.5 - 9 hours[118].

Some hydrogels and super-porous hydrogels offer a promising approach to gastric retention. These materials have a swelling ratio of over 1000[113]. They can be made by cross-linking water-soluble polymer chains or by polymerizing hydrophilic monomers in the presence of cross-linking agents. Super-porous hydrogels[119] have unique super-swelling properties combined with pore sizes in the range of few hundred micrometers to a millimeter. These materials can swell to the equilibrium size in less than 1 min., which is important requirement for gastric retention devices.

4.10.6. Pulsative or Timed-Release Drug Delivery System

Maintaining constant blood levels of a drug may not always be a desirable option for all types of diseases or ailments. Several circumstances exist in which varied blood levels of the drug during the course of therapy is preferred. For example, hypertension, diabetes mellitus, cardiac arrhythymia, and certain infections require varied concentrations of drug in blood according to the intensity of the disease and the physiological parameter being controlled. Thus, delivering drugs in a pulsatile fashion for certain clinical conditions is beneficial.

4.10.7. Targeted or Site-Specific Drug Delivery System

Delivering drugs to the desired site of action has several advantages, including reduced bio-burden and toxicity. Colonic drug delivery is gaining interest as one of the important targeted drug delivery systems. The objective of colonic drug delivery is not treat local diseases of the colon, but also to deliver certain deliver certain drugs such as proteins and peptides. Most colon-targeted systems are coated systems because of their wide acceptance, technological developments, and design flexibility.

4.10.8. Prodrug Drug Delivery System

A prodrug is a compound formed by chemical modification of a biological active compound, which will liberate the active compound *in vivo* by enzymatic or hydrolytic cleavage. The primary purpose of employing a prodrug for oral administration is to increase intestinal absorption or to reduce local side effects, such as *GI* irritation. Prodrugs can be used to increase the strategies for extended release and, in a limited sense, can be sustaining in their own right[120-122].

4.11. RELEASE CONTROLLING POLYMER AVAILABLE IN MARKET[95]

Materials used for controlling drug release from oral tablets and capsules include polymers from natural products, chemically modified natural products and synthetic products. Some of the common materials that have regulatory clearance are discussed briefly based on their applications in different types of controlled release systems.

4.11.1. Materials Used For Matrix System

the materials most widely used in preparing matrix systems include both hydrophilic and hydrophobic polymers. Commonly available hydrophilic polymers include hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), hydroxyethylcellulose (HEC), xanthan gum, sodium alginate, poly(ethylene oxide) and crosslinked homopolymers and copolymers of acrylic acid. They are usually supplied in micronized forms because small particle size is critical to the rapid formation of gelatinous layer on the tablet surface.

Hydroxypropyly methylcellulose is nonionic water-soluble cellulose ether made by Dow Chemical under the brand name of Methocel. Methocel is available in four different chemistries (E, F, J, and K series) based on varying degrees of

hydroxypropyl and methyl substitution. The specially produced Methocel of ultrafine particle size for controlled release formulations include K100LV, K4M, K100M, E4M and E100M. When dissolved at a concentration of 2% in water, the viscosity ranges from 100 to 100,000 cps. Similar grades of HPMC (Metolose SR) asre also available from ShinEtsu, Japan.

Hydroxypropylcellulose and hyroxyethylcellulose are nonionic water soluble cellulose ethers made by the Aqualon division of Hercules Inc. under the brand names Klucel and Natrosol, respectively. For controlled release applications they are available in high- and low-viscosity grades, such as Klucel HXF, EXF and Natrosol 250 CHX.

Xanthan gum is a water-soluble polysaccharide gum produced by the Kelco division of Monsanto Co. under the brand name of Keltrol. It is composed of D-glucosyl, D-mannosyl, and D-glucosyluronic acid residues and differing proportions of D-acetyl and pyruvic acid acetal. The primary structure consists of a cellulose backbone with trisaccharide side chains.

Sodium alginate is a water-soluble gelling polysaccharide also made by Kelco under the brand name of Keltone. Keltone HVCR and LVCR are forms that are used in controlled release products.

Poly(ethylene oxide) polymer is a nonionic water-soluble resins made by Union Carbide under the brand name Polyox. Its common structure is $-(OCH_2CH_2)_n - OH$. For controlled release applications it is available in a variety of viscosity grades. Examples include: Polyox WSR N-12K, WSR N-60K, WSR-301, WSR-coagulant, WSR-303, WSR-308 with molecular weights ranging from 100 to 8 million.

Crosslinked homopolymers and copolymers of acrylic acid are water-swellable but insoluble resins made by the B. F. Goodrich Company under the brand name Carbopol. Carbopol 971P NF, 974 P and 934 NF are specifically designed for preparing hydrogel and mucoadhesive controlled release systems.

Hydrophobic and monolithic polymer matrix systems usually use waxes and water-insoluble polymers in their formulation. Many waxes are long chain wax esters, glycerides, and fatty acids. Natural and synthetic waxes of differing melting points have been used as controlled release matrix materials. Examples include carnauba wax, bees wax, candelila wax, microcrystalline was, ozokerite wax, paraffin waxes, and low molecular weight polyethylene, to name a few. Insoluble polymers used in preparing controlled release matrices include fine powders of ammoniomethacrylae copolymers (Eudragit RL 100, PO, RS 100, PO) by Rohm America, Inc., ethylcellulose (Ethocel FP7, FP10, FP100) by Dow Chemical Co., Cellulose acetate (CA-398-10), cellulose acetate butyrate (CAB-381-20), cellulose acetate propionate (CAP-482-20) by Eastman Chemical Co. and latex dispersion of methacrylic ester copolymers (Eudragit NE30D).

4.11.2. Materials Used For Reservoir System

The most common materials to form a drug release barrier surrounding a core tablet, drug particles, beads, or pellets for diffusion-controlled reservoir systems include water-insoluble acrylic copolymers and ethylcellulose. These film-coating polymers have historically been used in an organic solution. In recent years, they have been mostly applied as aqueous dispersion that form films by a process of coalescence of sub-micrometer polymer particles. Ammoniomethacrylate copolymers (Eudragit RL 30D, RS 30D) are water-permeable and swellable film formers based on neutral methacrylic esters with a small portion of trimethylammonioethyl methacrylate

chloride. Methacrylate ester copolymers (Eudragit NE30D) is a neutral ester without any functional groups. They are supplied by Rohm America as 30% aqueous dispersions without the need of plasticizers unless improved film flexibility is desired. Ethylcellulose for film coating is available as an aqueous polymeric dispersion containing plasticizers under the brand name of Surelease (Colorcon) and as pseudolatex dispersion. Aquacoat ECD (FMC), which requires addition of plasticizers to facilitate film formation during coating.

Enteric polymers may also be incorporated into the coating film to modify release rate, such as cellulose acetate phthalate (CAP), hydroxypropylmethylcellulose phthalate (HPMCP), Methacrylic acid and Methacrylic esters (Eudragit L and S). Enteric polymers and pH-dependent polymers. At high pH (e.g., > 5.5), the polymer dissolves whereas at low pH, the polymer is impermeable and insoluble.

4.11.3. Polymers Used For Osmotic System

Cellulose acetate comprising a certain percentage of acetyl content can be used together with other pH-dependent and pH-independent soluble cellulose derivative to form a semipermeable film. Other polymers including polyurethane, ethylcellulose, poly (ethylene oxide) polymers, PVC, and PVA may be used in the osmotic system.

4.12. EXTENDED RELEASE DEVELOPMENT TECHNOLOGIES[95]

Almost all oral extended release systems are in the forms of tablets and capsules. Development technologies for these dosage forms include tabletting, pelletization, and film coating of single unit or multi-particulate.

4.12.1. Tabletting[123]

Extended release tablet dosage forms are usually manufactured using conventional processes of granulation such as wet granulation, dry granulation or direct compression. Granules prepared by wet granulation or dry granulation are sifted, lubricated and compressed into tablets while in case of direct compression the steps are blending and compression. The tablets may be further coated with functional membrane for controlling the release, stability or aesthetic purpose. Tablets can be compressed as multiple-layer for achieveing specific release.

4.12.2. Pelletization

Controlled release pellets, beads, or spheres may offer certain advantages over single unit dosage forms in that they minimize the risk of unexpected drug release (e.g., dose dumping), which may occur when a single-unit device is defective[124]. In addition, multi-particulate dosage forms can be designed to provide customized release profiles by combining beads with different release rates or to deliver incompatible drugs in the same dosage unit[125].

The basic methods for pellet or bead production include

(i) microencapsulation,

(ii) spray congealing,

(iii) formation of particles from a plastic mass, and

(iv) agglomeration.

Most microencapsulation techniques are based on processes by which coatings of natural or synthetic polymers are applied to solid or liquid agent via coacervation or polymerization[126-127]. The spray-congealing process consists of embedding the active drug in an excipient such as wax or plastic. Formulation of particles from a

plastic mass is achieved using a machine known as marumerizer or a spheronizer[128-129]. The spheronization process in the marumerizer involves partial shaping of pellets followed by utilization of friction and surface forces to form spheres. Powdered raw materials are converted into a plastic mass using water or solvents in conjunction with binding agents. This mass is extruded under pressure through a perforated screen or die. Spinning in the marumerizer the breaks down the cylindrical, spagnetti-like extrudates until the length is equal to the diameter. The process continues until they are rolled into spheres by centrifugal and frictional forces. To produce solid spheres, the extrudáte must break into short segments and short cylinders must be sufficiently plastic to be rounded by spheronization. The materials that break into short cylinders without sufficient plastic properties do not yield a spherical product[130]. microcrystalline cellulose is found to exhibit the elasticity required for extrusion and spheronization. Thus, it is an excipient most commonly used for pelletization / spheronization[131].

Agglomeration is one of the oldest process for manufacturing spherical particles. It is based on the layering technology derived from sugar coating in a coating pan. Traditionally, these spheronization processes involving surface forces can be divided into two stages: nucleation (seed growth) and sphere growth (bead preparation). With the layering technique, the active drug or other ingredients in the form of either a dry powder or solution /dispersion are agglomerated to form seeds. They are commercially available nonpareil seeds containing active drugs. This process can be performed in a coating pan, a rotary granulator, or a fludized bed.

4.12.3. Coating Technologies

In the pharmaceutical industry, significant advances have been achieved in polymer coating of solid dosage forms over the last two decades. Polymer coating involves

deposition of a uniform membrane of polymer ration onto the surface of the substrates, such as tablets, spheres, or pellets and drug particles. Coating techniques that are used in developing controlled release reservoir or osmotic systems include

(i) film coating,

(ii) layering coating and

(iii) compression coating.

Coating formulations as well as processing variables influence the properties of the resulting functional coating.

The film coating process is performed in a coating pan, a fluidized bed or a rotary granulator. Ethylcellulose, methacrylic ester copolymers, methacryl ester copolymers, cellulose acetate etc. are widely used either alone or in combination with water-soluble polymers for the preparation of controlled release films. Since, the integrity of the film and the absence of flaws or cracks are important factors in controlling the drug release from such preparation, it is imperative that the film formulation be optimized. Plasticizers are often added to such films to increase the film flexibility and minimize the incidence of flaws. Often factors affecting film coating and drug release include additives (e.g. pigment, plasticizer, solvent) and process variables (e.g., equipment, batch scale, airflow, spray rate, temperature).

The layering coating process is often performed in a coating pan or a fluidized bed coater. This type of coating process is not continuous. For example, in coating beads, the seeds may first be coated with one layer of active drug layer. The process is repeated until multiple layers are completed to meet the predetermined requirement. In some cases, the active drug may be dissolved or dispersed with the

coating materials. Factors affecting coating quality and performance of the final product are similar to those discussed in the film coating process.

The compression coating process is performed using a tablet press to make a compress coat surrounding a tablet core (tablet-in-tablet). The compress coat may function as a barrier to drug release or as a part of formulation to provide biphasic release. The process involves initial compression or the core formulation to produce a relatively soft tablet followed by transferring to a larger die for final compression of the compress coat layer. This process can be used to develop a controlled release product with unique release profiles or to formulate two incompatible drugs by incorporating one in the core and the other in the compress coat layer.

4.13. PRODUCT EVALUATION FOR DRUG AVAILABILITY

4.13.1. *In Vitro* Measurement Of Drug Availability

It is not possible to simulate in a single *in vitro* test system the range of variables that affect drug release during the passage of extended release medication through *GI* tract. Properly designed *in vitro* tests for drug release serve two important functions however. First, data from such tests are required as a guide to formulation during the development stage prior to clinical testing. Second, *in vitro* testing is necessary to ensure batch-to-batch uniformity in the production of a proven dosage form. Different methods are usually required by these two distinctly different testing situations.

Tests developed for the purpose of quality control are generally limited to USP dissolution testing methods using the rotating basket (Apparatus 1), the paddle (Apparatus 2), or the modified disintegration testing apparatus (Apparatus 3)[132]. In many instances in which USP test procedures are followed, upper and lower limits are specified for drug release in simulated gastric and/or intestinal fluid.

Measurements are made at specified time intervals appropriate to the specific product. Procedures are determined by nature of the dosage form (e.g., disintegrating or non-disintegrating), and the maintenance period. The methods used to measure drug release profiles should have the following characteristics. As far as possible the analytical technique should be automated so that the complete drug release profiles can be directly recorded. Allowance should be made for changing the release media from simulated gastric to simulated intestinal fluid at variable programmed time intervals, to establish the effect of retention of the dosage form is likely to encounter *in vivo*. In addition, the hydrodynamic state in the dissolution vessel should be controllable and capable of variation.

Besides, the USP dissolution testing apparatus, testing equipment used for extended action formulation have included the rotating bottle, stationary basket/rotating filter, Sartorius absorption and solubility simulator, and column type flow through assembly. The rotating bottle method was developed for evaluation of extended release formulations[133]. Samples are tested in 90 ml bottles containing 60 ml of fluid, which are rotated end over end in a 37 ^{o}C bath at 40 rpm. However, the method is not adaptable to automated analysis, or to easy manipulation of the dissolution media. The Sartorius device includes an artificial lipid membrane, which separates the 'dissolution' chamber from a simulated plasma compartment in which drug concentration are measured. Alternatively, a dialysis type membrane may be used. Systems of this type are advantageous in measuring release profiles of disintegrating dosage units and suspension, granular, and powdered material, if the permeability of the membrane is properly defined. The column flow through apparatus possesses similar advantages since drug release is confined to a relatively small chamber by highly permeable membrane filters. This apparatus is flexible, well defines, and meets all the necessary requirements for measurement of drug release profiles from extended release dosage forms. It can also be adapted to measurements under

near sink conditions if the release medium is passed only once through the dissolution chamber, directly measuring the rate of release. Alternatively the dissolution fluid might be recirculated continuously from the reservoir, allowing measurement of the cumulative release profile. The composition of the release media as well as the flow rate can readily be altered.

The time of testing may vary from 6 to 12 hours, depending on the design specifications of the dosage form. If formulations contain retardants whose function depends on the action of normal constituents of the *GI* fluids (e.g., bile salts, pancreatin and pepsin), then the appropriate materials must be included in the simulated release media. Apparatus of the Sartorius type would be advantageous in these circumstances if the analytical procedure for the drug would be adversely affected by the presence of these substances. Otherwise, the simulated fluids consisting of pH 1.2 and pH 7.2 buffers, as well as intermediate pH values, which represent the transition between gastric and intestinal pH would suffice at 37^{O}C. Drug release information are processed mathematically and graphically to understand the release kinetics. Confidence limits for the kinetic parameters can be calculated allowing establishment of limits for the percentage of released drug under limited testing conditions established for purpose of quality control. Comparison of results obtained with the same product using different testing methods as well as comparisons between multiple runs, different lots, and different products can be made more readily.

4.13.2. *In Vivo* Measurement Of Drug Availability

Validation of extended release product design can be achieved only by *in vitro* testing. The basic objective is to establish the bioequivalence of the product for which a controlled release claim is to be made with conventional dosage forms of the

formulated drug[134]. Since no necessary human testing should be done, animal models, such as dogs, should be used initially during the product development stage to tune the formulation to the desired specifications. It is necessary to verify that dumping or insufficient drug availability are not observed *in vivo*. Tests in both animal and subsequent human trials should include periodic blood levels determinations, comparisons of urinary excretions patterns, serial radiophotographs (in human) to follow the course of the dosage form in the *GI* tract, and sequential observations of pharmacologic activity. In some instances (e.g., with insoluble core tablets), ingested dosage forms should be recovered and assayed for drug content. If drug levels cannot be measured in biologic fluids, then the pharmacologic effect must be observed as a function of time, or clinical trials must be designed, to establish the effectiveness of the drug product.

The FDA has promulgated the general bioavailability and bioequivalence requirements for drug products[135]. These are made to ensure that the new drug formulation meets its controlled release claims, that no dose dumping occurs, that performance is consistent between individual dosage units, and that steady state drug levels obtained with the product are equivalent to currently marketed products with approved new drug applications (NDAs). Reference materials can include the pure drug substance in solution or suspension as well as conventional dosage forms administered according to their usual dosage schedules or according to the dosage schedule of the controlled release product. Bioavailability studies are ordinarily single dose comparisons of tested drug products in normal adults in a fasting state. A crossover design in which all subjects receive both the product and reference material on different days is preferred.

Guidelines for clinical testing have been published for multiple dose steady state studies as well as for single dose studies. Correlation of pharmacologic activity or

clinical evidence or therapeutic effective with bioavailability may be necessary to validate the clinical significance of controlled release claims.

While single dose studies are usually sufficient to establish the validity of extended release dosage form designs, multiple-dose studies are required to establish the optimum-dosing regimen. They are also required when differences may exist in the rate but not the extent of absorption, when there is excessive subject-to-subject variation or when the observed blood levels after a single dose are too low to be measured accurately. A sufficient number of doses must be administered to attain steady state blood levels.

4.13.3. *In Vitro In Vivo* Correlation[136]

Attempts to correlate *in vivo* performance with *in vitro* availability tests generally have been based on 'single point' measurements. For example, AUC values, peak blood levels or peak times might be correlated with the time required for 50% of drug to be released *in vitro*. The best that can be expected from this approach is a rank order correlation. Significantly bioavailability difference between formulations might be masked by improper *in vitro* methods, or drug release studies might indicate a greater difference than is actually seen *in vivo*.

Two general approaches interrelating *in vivo* and *in vitro* measurements of drug release have been suggested. In one approach, an *in vitro* release profile is transformed into a predicted *in vivo* response. A weighting function characterizing a reference product is determined between the release profile and the average *in vivo* response, which is measured in a panel of human subjects by the mathematical operation of deconvolution. The *in vivo* response, predicted *in vitro*, of the dosage form undergoing testing is obtained by convolution of the observed release profile and the weighting function.

The technique is computationally complex but maximizes the amount of information derived from *in vitro* dissolution testing[137]. Alternatively , a reference blood level profile is used as the input to a feedback controlled dissolution testing apparatus, which is subsequently forced to yield a release profile close to the standard by dynamically changing release media and flow rates. The conditions established using the reference product is used for testing other formulations. Applications of these techniques to extended release products require a similar formulation as the reference.

In the second approach, the apparent *in vivo* drug release profile is computed from smoothed blood level or urinary excretion data[138]. This technique requires knowledge of the pharmacokinetic model of the drug. The *in vivo* data are used as input to a computer simulation of the pharmacokinetic model; the output represents the amount of drug released at the absorption site as a function of time. *Beckett*, in applying this method to a extended release form of phendimetrazine, found that measured *in vitro* release rate were significantly faster than computed *in vivo* release rates[138].

In vivo testing involves a number of simplifying assumptions regarding the uniformity of the absorption process and suitability of using average data points to represent the population. Since the formulator has no control over physiologic variables, it is essential that clinical studies be based on sufficiently large cross sections of the population to provide meaningful results. Both *in vivo* and *in vitro* testing methods play a major part in validating the effectiveness of extended release formulations.

4.14. STABILITY STUDIES

As with all pharmaceutical dosage forms, stability testing is an important aspect of the development stage. The same standards that apply to conventional dosage forms with respect to stability of active ingredient and dosage form integrity should be used. The stability-testing program includes storage of the formulation under both normal (shelf) and exaggerated temperatures and other conditions, so that appropriate extrapolations for long term stability can be made. The stability of the release profile in addition to that of the active ingredient must be assessed.

Most ER formulations are complex. They may be formulated with ingredients that often present special problems regarding their physical stability upon storage. Further, more accelerated stability testing may induce changes in some systems. (e.g., polymorphic or amorphous to crystalline transitions); these changes would not be observed under normal shelf storage conditions. In additions, observed release profiles measured after storage at elevated temperatures reflect loss of drug due to degradation. Consequently, predictions of long term release profile stability based on accelerated tests could lead to erroneous conclusions. The stability-testing program for an ER product cannot be outlined specifically. It depends on the dosage form and its composition.

4.15. REGULATORY CONSIDERATIONS IN EXTENDED RELEASE DRUG DELIVERY SYSTEMS

The regulatory requirements[10] related to controlled release dosage forms, appeared first in the regulation that was published thirty years ago by the US FDA. It defined the conditions under which drugs delivered to patients in a controlled release formulation over a prolonged period would be regarded as new drugs. As with new drugs in conventional dosage forms, the regulatory approval for a controlled release

pharmaceutical product (or drug delivery system) requires submission of scientific documents form pharmaceutical firms to substantiate the clinical safety and efficacy of the controlled release drug delivery system and to demonstrate its controlled release characteristics[139].

To demonstrate the safety and efficacy of a controlled-release formulation (or drug delivery system) controlled clinical studies may be required to be done along with the standard with regard to effectiveness and side effects. Without appropriate clinical studies, the label cannot be modified. Bioavailability studies are required to be performed under steady-state conditions to demonstrate approved comparatively to an approved immediate-release drug product.

The firms are also called to furnish information regarding the following point:

- The product meets the controlled release claims made for it.
- The bioavailability profile established for the product rules out the occurrence or dose dumping.
- The product's steady-state performance is equivalent to that of currently marketed non-controlled release pharmaceutical products that contain the same active ingredient.
- The product's formulation provides consistent pharmacokinetic performance between individual dosage units.

For comparative studies, the following preparations are generally used.

- A solution or suspension of the same active drug ingredient.
- An approved non-controlled release pharmaceutical product containing the same active drug moiety.

- An approved controlled release formulation containing the same active ingredient in the same concentration and same form (e.g. Tablet, Capsules, etc.).

To demonstrate the controlled release characteristics of drug(s) delivered from an ER pharmaceutical product, the information is required to be submitted includes:

- *In vitro* drug release data highlighting reproducibility of method, proper choice of medium, maintenance of perfect sink conditions and good control of solution hydrodynamics. Also, a meaningful *in vitro* /*in vivo* correlation should have been established.
- *In vivo* bioavailability data highlighting the pharmacokinetic profiles, data comparable to already marketed preparations and supporting the label claims and reproducibility of *in vivo* performance.

In addition to safety and efficacy, considerations of such new drug delivery systems, biopharmaceutics and pharmacokinetics issues need to be addressed by the manufactures. The key elements that need to be established are as follows:

- Reproducibility of drug release kinetics.
- A defined bioavailability profile that rules out the possibility of dose dumping.
- Demonstration of reasonably good absorption relative to an appropriate standard.
- A well-defined pharmacokinetic profile that supports drug labeling.

4.16. POST APPROVAL CHANGES

Following the successful launch of a new product, it is not uncommon for development scientist to make continuous effort to improve its quality or to reduce its manufacture cost. The modifications typically involve changes in the formulation components or compositions, the site of manufacturing, scale-up or scale-down of the manufacturing process and/or equipment. The issues involved in these changes of controlled release products are different and usually more complex than their IR counterparts. Thus, the FDA issued a separate guidance on the scale-up and post approval changes (SUPAC) for modified-release solid dosage forms in Sept. 1997[140]. Based on fundamental pharmaceutical principles and the scientific database, acceptable ranges of these changes are defined and categorized into three different levels on their likelihood of having significant impact on the product quality and performance.

Additional in process and finished product control parameters are also specified for used in supporting these changes. Formulation and process changes discussed in this section are mostly based on SUPAC Guidance for modified-release solid oral dosage forms published by the Center for Drug Evaluation Research, Food and Drug Administration.

4.16.1. Formulation Changes

For modified-release solid dosage forms, consideration should be given as to whether the excipient is critical or not critical to drug release.

4.16.1.a. Non-Release Controlling Excipient

Three levels of changes for non-release controlling excipients are defined as follows:

- Level 1 changes are those that are unlikely to have any detectable impact on formulation quality and performance.
- Level 2 changes are those that could have a significant impact on formulation quality and performance.
- Level 3 changes are those that are likely to have a detectable impact on formulation quality and performance.

4.16.1.b. Release Controlling Excipient

The changes for the release-controlling excipient are categorized into three levels similar to the non-release controlling excipients:

- Level 1 changes are those that are unlikely to have any detectable impact on formulation quality and performance.
- Level 2 changes are those that could have a significant impact on formulation quality and performance. Test documentation for level 2 changes would vary depending on whether the product could be considered to have a narrow therapeutic range.
- Level 3 changes are those that are likely to have a detectable impact on formulation quality and performance affecting all therapeutic ranges of the drug.

4.16.2. Process Changes

If the manufacturing process that is not identical to the original manufacturing process used in the approved application is to be used, appropriate validation studies should be conducted to demonstrate that the new process is similar to the original process. For oral controlled release dosage forms, consideration should be given to

whether or not the change in manufacturing process is critical to drug release. Three levels of process changes are defined as follows:

- **Level 1 Changes:** This category includes process changes involving adjustment of equipment operating conditions such as mixing times and operating speeds within original approved application ranges affecting the non-release -controlling and /or release -controlling excipient(s).
- **Level 2 Changes:** This category includes process changes involving adjustment of equipment operating conditions such as mixing times and operating speeds outside the original approved application ranges.
- **Level 3 Changes:** This category includes changes in the type of process used in the manufacture of the product, such as a change from wet granulation to direct compression of dry powder.

4.17. EXTENDED (SUSTAINED/ CONTROLLED) DRUG DELIVERY – TODAY AND TOMORROW[141-146]

There is a little doubt that newer drugs, including gene therapy, are intended to treat the cause of a disease rather than the symptoms. These newer drugs have inherent disadvantages of size, usually sufficiently large to slow or inhibit membrane permeability, sensitivity in dose and dosing regimen, commonly potent drugs needing short exposure time to target receptor, and then being quite unstable to external environment. One can develop a short list of needed technologies. Carriers to assist membrane permeability. The carriers can be tissue friendly, classic penetration enhancers, or preferably modeled after the physiologically based chaperones, e.g. macromolecules.

Biocompatible – Bioerodible Injectable Polymers: A sizable number of non-toxic, erodible polymers possessing a range of physicochemical properties are

needed to embrace the diverse properties of new and emerging drugs. These drugs include microencapsulation and transplantation of endocrine tissue.

Stimuli-Sensitive Polymers: These polymers respond to pH, temperature and electrochemical stimuli as well as to more subtle specific biochemical triggers. Such intelligent polymers are necessary for feedback controlled drug delivery systems.

Kinetic- And Equilibrium-Modulated Polymers: The need for cycling in release rate is essential for many drugs. Such flexibility in polymers is currently at a primitive stage.

Platforms For Tissue Engineering: There is need for biocompatible casing for all transplants, polymer composites for patching wounds, scaffolds that guide and encourage cells to form tissue bioreactors for large-scale production of therapeutic cells. From this list, a number of issues become instantly apparent. First, drug delivery is a multidisciplinary activity involving polymer scientist, pharmaceutical scientists, chemical engineers and a variety of biologically oriented scientists. Second, the trend to produce polymers possessing multiple properties, depending on the environment, highly specialized function is apparent. Third, the driving force for most of these changes is an expanding understanding of biology as it pertains to drug delivery systems. If last two decades represent the period to define what is needed in controlled drug delivery and understand, even at an organ level, disposition tissues for the various routes of administration, next two decades will represent the true biomedical polymer period. Of course, success of this period is dependent on continued economic success of drug delivery systems and the willingness of certain companies or entrepreneurs to invest in this future.

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Chapter 5

Literature Survey...

5.1. A REVIEW - EXTENDED RELEASE CARDIOVASCULAR DRUGS THROUGH HYDROXYPROPYL METHYLCELLULOSE

5.1.1. INTRODUCTION

ı the rapidly developing field of medical technology, novel polymeric matrices have been used as Extended Release (ER)/Controlled Release (CR) devices for a variety of drugs. Among these, the water insoluble and swellable, hydrophilic polymers, also called hydrogels, are used as drug delivery devices for the controlled release of active agents[1-4]. The release of a drug is generally controlled by one or more of the processes: namely, the molecular transport of solvent into the polymer matrix, swelling of the polymer, erosion of the swollen polymer, diffusion of the drug through the swollen polymer alteration of, physico-chemical properties (solubility, viscosity, etc.) of the drug and of the polymers, drug/polymer composition, formulation, administration form, etc. It is rather a difficult task to achieve the constant dissolution rate from the ER devices because the dissolution patterns generally show a diffusion dependent (*Fickian*) release transport. However, the drug release from a hydrophilic swellable polymer depends on both the polymer relaxation rate and the drug diffusion from the barrier. Generally, the surface of the hydrated gel forms a thin barrier for the drug release to take place, which is linearly related to the exposed external surface area of the swollen matrix. The formation of such a barrier layer becomes extremely critical to the success or failure of the dosage form as a ER device[5].

In the ER of a drug through the polymer matrices, the ultimate goal is to maintain the therapeutic level of the drug in the blood. The major efforts in this area have been to achieve the zero-order release kinetics through one or many of the approaches namely

(i) Use of rate controlling barriers;

(ii) Freezing in a non-uniform concentration profile of the drug across the matrix;

(iii) Modification of the geometry of the polymeric device;

(iv) Swelling-controlled delivery systems based on glassy hydrogels;

(v) Copolymerization with hydrophilic monomers; and

(vi) Hydrogel design which rupture during the course of drug release.

In recent years, there has been tremendous research activity on the ER of cardiovascular drugs through the cellulose ether based matrices, but the literature on this subject is widely scattered. The concept of poly-pharmacy, i.e., drug combination therapy, is also gaining universal acceptance, even in the treatment of hypertension[6].

Recent studies have shown that HPMC, a water-soluble polymer, is being frequently used in the formulation of ER dosage forms for the cardiovascular drugs. The mechanism by which HPMC retards drug release includes its ability to form rapidly a gel layer at the matrix periphery exposed to the aqueous fluid. The drug is then released from the matrix by a combination of drug diffusion and erosion of the gel. Drug diffusion through HPMC matrix therefore depends on its water solubility, though the drug release can be modified by changing several formulation factors such as the type of excipients, presence of surfactant and viscosity of HPMC.

The use of HPMC as an ER system has been well documented[7-18]. *Hogan*[19] reviewed the use of HPMC in pharmaceuticals. The release of drugs from compressed HPMC matrices was reviewed by *Alderman*[20]. The release of drugs from HPMC matrices in terms of the mechanisms and technological factors has also been documented[21, 22]. From a perusal of the literature, it is observed that the mechanism proposed for the ER of HPMC matrices involves the liquid penetration into the dry matrix, hydration and swelling of HPMC, diffusion of the dissolved drug

and erosion of the polymer layer. Although extensive research has been carried out to study the type and nature of HPMC on drug ER properties, a study on the effect of liquid transport properties into such matrices has been somewhat neglected. *Ranga Rao et al*[23] published a review on the swelling controlled SR systems. The polymers covered in this review are: poly(hydroxylalkyl-methacrylates), polyvinyl alcohol, poly(ethylene oxide), polyethylene glycol and cellulose ethers such as HPMC and NaCMC.

5.1.2. KINETICS OF SWELLING OF HYDROGELS AND THE EXTENDED RELEASE PHENOMENON

Hydrogels are the hydrophilic network polymers, which are glassy in the dehydrated state and swell when come in contact with the aqueous media. In the presence of water, hydrogels absorb a significant amount of water to form the elastic gels. Since their introduction 20 years ago, synthetic hydrogels have been increasing in popularity in various biomedical/pharmaceutical applications ranging from soft contact lenses to drug delivery systems[24-28]. In addition to their inertness and good biocompatibility, their ability to release the entrapped drug in aqueous medium and the ease of regulating such drug release by controlling water swelling rate and the crosslinking density made these hydrogels particularly attractive as the ER devices for pharmaceutical products.

In many oral delivery applications, drug-loaded hydrogels are usually stored in the dry, glassy state due to stability requirements. The release of water-soluble drugs from such dehydrated hydrogel matrices generally involves the simultaneous absorption of water and desorption of the drug via swelling-controlled diffusion mechanism[29, 30]. As the water penetrates into a glassy hydrogel matrix containing the dispersed drug, the polymer swells and its glass transition temperature, T_g, is

owered. At the same time, the dissolved drug diffuses through the swollen rubbery region into the external releasing medium. Such diffusion and swelling phenomena generally do not follow the *Fickian* mechanism[32], but the polymer relaxation rate, in addition to drug diffusion is believed to be responsible for the observed non-*Fickian* behavior. If a polymer is thermodynamically compatible with the solvent, then its T_g is lowered below the experimental temperature so that the hydrogel swells to a rubbery state, which is accompanied by an expansion of volume. *Fickian* diffusion is generally characterized by a square root of time dependence in both the amount of liquid diffused and the penetrating diffusion front position. On the other hand, case-II transport, which is completely governed by the rate of polymer relaxation, exhibits linear time dependence in both the amount diffused and the penetrating swelling front position. However, cast II diffusion due to the balance polymer relaxation and solute diffusion was first introduced by *Hopfenberg*[33] using gels swelled in organic media. Later, this phenomenon was confirmed in hydrogels by several researchers[33-36]. In most of the cases however, an intermediate situation, often called the non-*Fickian* or anomalous diffusion, exists whenever the rates of *Fickian* diffusion and polymer relaxation are comparable[37-41].

Often the following empirical equation has been used[42,43] to express the fraction of drug released during the initial short-time period:

$$\frac{M_t}{M_\infty} = Kt^n \qquad (1)$$

where, M_t denotes the diffusant released at time *t* and M_∞ denotes the diffusant at infinite time i.e., after attainment of equilibrium. *K* is a constant characteristic of the polymer-drug system and *n* is an exponent characteristic of the mode of transport. For $n = 0.5$, the drug release follows the well-known *Fickian* diffusion. If *n* varies between 0.5 and, then non-*Fickian* (or anomalous) diffusion is observed. The special case of $n \geq 1$ gives rise to a case-II transport, which is of particular interest because

the drug release from such devices having constant geometry will follow the zero-order kinetics, a preferred phenomenon in the SR studies[44-46].

From the foregoing discussion, it is apparent that there is a strong link between the polymer structure and the drug transport regime. Thus, the penetrant uptake has been exploited as a probe to study the polymer structure. However, the methods traditionally applied to follow the transport kinetics in polymers provide only limited information. Gravimetric techniques such as direct weighing used by *Aminabhavi et al*[37, 41, 47, 48] have been most commonly employed. While these methods measure absorption and desorption rates, but they can give only indirect information about the structural changes in polymers and the drug-polymer interactions. However, more detailed information could be obtained using sophisticated techniques such as Electron Spin Resonance (ESR)[49-51], optical microscopy[43, 46, 52] and *Rutherford* Back-scattering Spectrometry (RBS)[53]. These techniques are indirect as they require doping or contrasting agents and are often invasive or destructive. RBS, for example, requires the polymer in the form of a film of a few μm thick and the penetrant must contain an element, such as chlorine or iodine, to which RBS is sensitive.

In order to calculate the values of diffusion coefficients, *D*, of the drug from the polymer matrices, the initial sorption data from a graph of M_t/M_∞ vs. $t^{1/2}$ have been used to compute *D*[32]:

$$D=\frac{\pi}{16}(\theta)^2 \tag{2}$$

with $\theta=\frac{d[M_t/M_\infty]}{d\left(\sqrt{t}/h\right)}$. Here, *h* is the thickness of the polymer layer and θ is the initial slope of the linear portion of the sorption plot. In addition to equation (1) and (2), the *Higuchi* relation[54] has also been used to analyze the experimental ER data.

$$M_t = \left[(2A - C_p) C_p D_t \right]^{1/2} \qquad (3)$$

where M_t is the amount of drug released per unit surface area in time *t*, *A* denotes the initial amount of loading, C_P is solubility of the drug in the rubbery matrix, and *D* is diffusivity of the active ingredient in the matrix. The derivation of *Higuchi* equation was based on the pseudo steady-state analysis. As a result, the predictions of release rates are in error by up to 11.3 5 in the limit $A \rightarrow C_P$.

Paul and *McSpadden*[55] subsequently offered an exact analysis for the release of an active ingredient that is physically dispersed/dissolved in the polymer matrix. Thus,

$$M_t = \frac{2C_P}{erf(\eta^*)} \sqrt{\frac{Dt}{\pi}} \qquad (4)$$

where $\eta^* = \dfrac{\xi}{2\sqrt{Dt}}$ and

$$\sqrt{\pi}\,\eta^* \exp\left(\eta^{*2}\right) erf(\eta^*) = \frac{C_P}{A - C_P} \qquad (5)$$

ξ denotes the thickness of the region within which the concentration of the drug decreasing from *A* on the surface of the undissolved solute core within the matrix to zero at the surface of the matrix. When the drug is dissolved in the matrix, i.e., $A \rightarrow C_P$, we have

$$M_t = 2C_P \left(\frac{Dt}{\pi}\right)^{1/2} \qquad (6)$$

If drug is dispersed in the matrix, i.e. $A >> C_P$,

$$M_t = [2DC_P(A - C_P)t]^{1/2} \qquad (7)$$

This is the same as Eq. 3 except for the coefficient 0.5 for C_P, which is of little significance in the limit $A >> C_P$.

Higuchi[56] also deduced another ~~relation for the perce~~ntage of drug released from one side of a layer of ointment in which the drug is initially uniformly dissolved. The percent drug released, *R*, is then given as

$$R = \frac{100Q}{hC_0} = 100\left[1 - \frac{8}{\pi^2}\sum_{m=0}^{\infty}\frac{1}{(2m+1)^2}\exp\left(-\frac{D(2m+1)^2\pi^2 t}{4h^2}\right)\right] \quad (8)$$

where Q is the amount of drug released per unit area of application, C_0 is the initial concentration of the drug in the ointment, D is the diffusion coeffic'^nt of the drug in the ointment, t is time after application and m is an integer, which varies from 0 to ∞. Equation (8) is a solution of Fick's law described elsewhere[57,58]. The main assumptions involved in equation (8) are: (i) only a single type of drug is present in the ointment; (ii) D must be constant with respect to both time and position in the ointment layer; (iii) only drug diffuses out of the layer, i.e., components of the vehicle cannot diffuse out (or evaporate); and (iv) the drug reaching the receptor side of the ointment layer is removed rapidly (this is the same as the boundary condition i.e., the concentration of drug is zero at receptor-ointment boundary for $t > 0$).

As a criterion to predict whether the drug transport in a polymer is diffusion or relaxation-controlled, *Vrentas et al*[59] defined the diffusion *Deborah* number (*DEB*) as

$$DEB = \frac{\lambda_m}{\theta} \quad (9)$$

where λ_m is mean relaxation time of the polymer-solvent system and θ is a characteristic diffusion time defined by h^2/D. In this case, the sample dimension, as well as composition and temperature is important in determining the transport mechanism. For (*DEB*) $\leq$ 1 or (*DEB*) $\geq$ 1, *Fickian* diffusion will occur either the rubbery or glassy state, respectively. When (*DEB*) $\approx$ 1, non-Fickian (anomalous) diffusion including case-II transport is anticipated depending upon the relative importance of the *Fickian* diffusion and the polymer-relaxation processes. An estimate of drug loading was calculated by assuming that the drug is dissolved in all of the gel water and that its concentration in the gel water is the same as in the external solution. Thus,

$$\% \, Drug = \frac{C_S V}{W_{dd}} \times 100 \qquad (10)$$

where C_S (in mg/ml), V (in ml) and W_{dd} (in mg) are the saturation concentration of the drug in water, the volume of water in the swollen gel, and the weight of the dry drug-loaded gel, respectively.

A conservative criterion for the zero-order release mechanism has been proposed by *Peppas* and *Franson*[42] in terms of the equilibrium swelling interface number, S_w defined as:

$$S_w = \frac{V_{max} h_{max}}{D} \qquad (11)$$

where V_{max} denotes the maximum velocity of the penetration front and h_{max} is the equilibrium thickness of the membrane. Based on the extrapolation of the plot of S_w vs. the exponent value, n of equation (1), it can be postulated that zero-order release occurs for $S_w << 1$. *Lee*[60] also proposed a mathematical model for the release of a drug from swellable glassy hydrogels in which the drug is uniformly distributed. This model envisages a time dependent diffusion coefficient for the drug to account for the role of molecular relaxation in the diffusion process. Based on the solution of diffusion equation, it was predicted that for a value of the *Deborah* number for the release greater than unity DEB ≅ 10, zero-order release would be observed. Thus, the dimensionless parameters DEB and S_W are important in the conceptual understanding of the various diffusion mechanisms. However, only very limited experimental determination of S_W has been attempted[42].

5.1.3. CARDIOVASCULAR DRUGS

In general, any drug that affects the heart or blood vessels, directly or indirectly, is a cardiatonic or antihypertensive drug, although this term generally connects only those drugs, which are used for their cardiovascular activity. Many such drugs are

available presently in the market and they display pronounced daily variations in their functions as well as in its hormonal and biochemical regulatory mechanisms[61-64]. Nearly all groups of antihypertensive drugs show a circadian phase dependency in their effects. The British National Formulary[65] gives an extensive list of these drugs, and some important cardiovascular drugs are listed in Table 5.1. In addition to those given in Table 5.1, there are other drugs such as anticoagulants and protamine, antiplatelet, fibrinolytic, antifibrinolytic and hemostatics, lipid lowering drugs etc.

Table 5.1. Cardiovascular drugs[65].

Drug Type	Examples
Vascodilators	Diazoxide, Hydralazine hydrochloride, Sodium nitroprusside, Minoxidil
Centrally acting anti-hypertensive drugs	Clonidine hydrochloride, Methyldopa
Adrenergic neurone blocking drugs	Guanethidine monosulfate, Bethanidine sulfate, Debrisoquine
Alpha-adrenoceptor blocking drugs	Prazosin hydrochloride, Doxazosin, Tetrazosin, Phenoxybenzamine hydrochloride, Indoramin, Phentolamine mesylate
Angiotension-converting enzyme inhibitors (ACE inhibitors)	Captopril, Cilazapril, Enalapril maleate, Fosinopril, Lisinopril, Perindopril, Quinapril, Ramipril, Trandolapril
Ganglion-blocking drugs	Trimetaphan camsylate
Tyrosinehydroxylase inhibitor	Metirosine
Nitrates	Glyceryl trinitrate, Isosorbide mononitrate, Isosorbide dinitrate, Pentaerythritol tetranitrate
Calcium channel blockers	Amlodipinebesylate, Diltiazem hydrochloride, Felodipine, Isradipine, Lacidipine, Nicardipine hydrochloride, Nifedipine, Nimodipine, Verampil hydrochloride
Peripheral vascodilators	Cinnarizine, Nafidrofuryl oxalate, Nicotinic acid derivatives, Oxpentifylline (Pentoxifylline), Thymoxamine, Adrenaline, Dobutamine hydrochloride, Dopamine hydrochloride, Dopexamine hydrochloride, Isoprenaline hydrochloride, Xamoterol, Ephedrine hydrochloride, Metarminol, Methoxamine hydrochloride, Noradrenaline acid tartrate, Phenylephrine hydrochloride

The polymer, HPMC have often been used to prepare the ER matrix tablets because the polymer is nontoxic, easy to handle and does not require any special manufacturing technology for their large-scale production. A list of such excipients used commonly in the pharmaceutical industries is given in Table 5.2.

Table 5.2. Typical cellulose-based excipients used in the pharmaceutical industries.

Excipient	Application
Calcium carboxymethylcellulose	Disintegrant
Sodium carboxymethylcellulose	Disintegrant
Microcrystalline cellulose	Binder, diluent, disintegrant
Methyl cellulose	Binder
Ethyl cellulose	Binder, coating material
Hydroxyethylcellulose	Binder, film former
Hydroxypropylcellulose	Binder, granulating agent
Hydroxypropyl methylcellulose	In SR formulations, film former
HPMC phthalate	Binder in the preparation of granules with SR properties

5.1.4. DISCUSSION OF LITERATURE RESULTS

In this section, the published results on HPMC based hydrogel matrices where in HPMC alone or in combination of other polymers used as ER devices are critically evaluated.

5.1.4.i. Propanolol hydrochloride

Propranolol hydrochloride is a non-selective β-blocker antihypertensive drug. It has a short elimination half-life of 3 h, which makes it a suitable candidate to be delivered at a controlled rate. Hydrogel matrix SR tablet formulations containing propranolol hydrochloride were prepared by *Ganga et al*[2] using HPMC, Na CMC and their

various combinations to evaluate the *in vitro* release kinetics and to study the therapeutic effects in mongrel dogs. A calculated amount of the drug and hydrogels were mixed and compressed into tablets using a Manesty E2 single punch hand operated tablet machine using flat-faced punches at a compression pressure of 16 tons psi. Specifications for the six batches of matrix tablets are given in Table 5.3.

The dissolution results were analyzed by measuring UV absorbance at 290 nm and the release rate constants were calculated for the first- and zero-order release kinetics as well as *Higuchi* equation. These data are also included in Table 5.3. Neat propranolol tablets released nearly 94% of the drug within 2 h. However, the zero-order release kinetics were seen for a selected drug, HPMC, and Na CMC combination. In dogs, the ER tablet showed 50% inhibition of isoprenaline-induced tachycardia after 2 h, which was maintained up to 4 h. At the end of 8 h, 33% inhibition of tachycardia was observed. The neat tablet showed a maximum inhibition of 60% for up to 2 h. By the end of 8 h, the dog's heart rate returned to normal. It was concluded that the hydrogel matrices provide the ER propranolol to produce improved therapeutic effects in dogs.

In a recent study by *Bodea* and *Sorin*[66], optimization of the release rate of propranolol hydrochloride from mixtures containing HPMC and Na CMC with the drug were designed. These experimental data were evaluated using a quadratic model to generate contour plots so as to assess the change in response surface to establish the relationship between dependent and independent variables. In another study[67], the effects of hydrophilic polymers on the ER of propanolol hydrochloride as a function of the drugs solubility was investigate. The release rates were analyzed theoretically.

Table 5.3. Batch specification and propranolol hydrochloride content of the tablets[2].

Drug/polymer ratio	Tablet Drug Content (mg)	Rate constants		
		k_1	k_0	k_h
Plain tablet	39.98	—	—	—
Drug:HPMC (1:5)	40.00	-0.035	5.20	0.254
Drug:HPMC (1:3.5)	40.00	-0.048	5.97	0.253
Drug:Na CMC (1:4)	40.20	-0.074	7.46	0.254
Drug:Na CMC (1:6)	40.20	-0.055	6.84	0.254
Drug:HPMC:NaCMC (1:2:5)	40.60	-0.067	8.62	0.254
Drug:HPMC:NaCMC (1:0.5:3)	40.00	-0.075	8.75	0.254

k_1 - First order dissolution rate constant
k_0 - Zero-order dissolution rate constant
k_h - Higuchi equation dissolution rate constant

Recently, *Perez-Marcos et al*[68] examined the potential of combining HPMC (Methocel K 4M) and Carbomer 974 (Carbopol 974) to extend the dissolution rate and to rationalize the role played by the polymers in the ER of propranolol hydrochloride from the matrix tablets. The tablets of 12.7 mm flat-faced were directly compressed at 197 MN/m^2 using the Manesty F_3 tableting machine. Tablets contained 160 mg of propranolol hydrochloride, 40, 90 or 140 mg of polymer; and 0.75% magnesium stearate as the lubricant. The ratios of polymer used were 0:1, 1:2, 1:1, 3:1 or 1:0 HPMC/Carbopol 974. Dissolution was studied at 100 rpm at 37^{O}C and the results were analyzed at 288 nm using UV-spectrophotometry. The dissolution rates were quantified by treating the data as a function of square root of time. For HPMC/Carbopol ratio, the dissolution rate of propranolol decreased as the amount of total polymer increased (see Table 5.4). Similar dissolution rates were found from the data corresponding to 5-35% of the total drug release from matrices containing the same weight of the polymer, but a burst release occurred from formulations

containing 1: > 3 HPMC/Carbopol 974, once 35% of the drug had dissolved. Increased quantities of free water in the gels were observed, producing a reduction in viscosity. Hydration studies on Carbopol 974 gels and matrices indicated that two different types of water were present in the scans of melting process. Also, the amount of water imbedded for Carbopol 974 was lower than by HPMC or 1:1 mixture of the polymers. The burst release during dissolution was explained by the formation of a complex between propranolol hydrochloride and Carbopol 974. Dissolution rates in the range of 5-35% were independent of the polymer ratio. The mechanism of drug release was analyzed by using the relation

$$\frac{M_t}{M_\infty} = K\left(t - t_0\right)^n \tag{12}$$

where K is a kinetic rate constant, t is release time, t_0 denotes the lag-time prior to dissolution and n is the exponent indicative of the mechanism of release. Values of $n \cong 0.6$ indicated the release to be diffusion-controlled to zero-order release.

Wan et al[8] examined the kinetics of matrix swelling using the coupled case-I and case-II equations. Matrices were prepared from varying concentrations of one to four different viscosities of HPMC with either propranolol hydrochloride or ibuprofen and were evaluated for swelling by determining the vertical displacement using a dial

Table 5.4. % Dissolution rates/min$^{1/2}$ of propranolol hydrochloride from HPMC/Carbopol 974 matrices and their mixtures[68].

Ratio of HPMC/Carbopol	Amount of polymer (mg)		
	40	90	140
1:0	7.33	5.02	4.06
3:0	6.51	4.34	3.81
1:1	6.86	4.75	3.74
1:3	6.94	4.10	3.46
0:1	6.65	4.73	3.93

indicator. The thickness of the swollen layer formed around. the matrix core increased with the viscosity of HPMC gel. The dynamic swelling results of this study were analyzed by using the empirical relation similar to equation (1) i.e., log $\delta = n$ log $t + K$, where $\delta = [(h_s-h)/h] \times 100$ is the swelling index calculated from the initial thickness h and the swollen thickness h_S of the membrane, n is exponent describing a *Fickian* or anomalous swelling mechanism and K is a constant. For the HPMC-propranolol matrices, the swelling mechanism in water was non-*Fickian* with an increasing amount of HPMC. This indicated the increasing importance of case-II relaxational mechanism to the overall matrix swelling. The coefficients of both case-I and case-II mechanisms increased with increasing concentration of HPMC. However, the effect of HPMC concentration on swelling rates was less marked at higher polymer content, i.e., > 50% of HPMC of high viscosity grade and a saturation state was attained beyond 40% of HPMC content of these matrices.

Wan et al[69] also studied the liquid penetration profiles of HPMC/drug matrices using propranolol hydrochloride and ibuprofen as model drugs. In this study, a special apparatus developed earlier[70] based on the capillary tube method was used to measure the volume of the liquid penetrated into the matrix after time t. They fitted the results to the simple *Washburn* equation[71]:

$$V = k^m t^m \qquad (13)$$

where V is volumetric uptake by the matrices, m=0.5, t is time of release and k is a constant. The liquid uptake kinetics data was analyzed using the relation:

$$V = k_1 t^m \qquad (14)$$

where m is an exponent describing *Fickian* anomalous uptake. The *Washburn* equation failed to describe fully the liquid penetration into a matrix system compressed with a swelling polymer. A polynomial equation incorporating *Fickian* case-I diffusion and case-II relaxational models was found to be more appropriate. An increase in the polymer content shifted the ratio of contributions toward an

increase in case-I and a decrease in case-II contributions to the overall uptake. It was concluded that a polynomial equation incorporating the *Fickian* case-I diffusion and case-II relaxational models have been used successively to describe the liquid penetration rates into the HPMC matrices.

In view of the importance of chirality in pharmaceutical research[72, 73], a study was conducted by *Duddu et al*[74], on the release of propranolol hydrochloride enantiomers from a chiral HPMC formulation using high-performance liquid chromatography (HPLC). The release of propranolol enantiomers from HPMC matrices, although variable, was found to be stereoselective. The S:R enantiomer ratio was 1.07 and this was due to stereoselective diffusion of enantiomers through the chiral environment of the hydrated matrix and/or stereoselective complexation of the enantiomers with the hydrated chiral polymer. On the other hand, the release of enantiomers from the β-cyclodextrin complex was not stereoselective. It was concluded that the release of propranolol enantiomers was from HPMC matrices, but not from β-cyclodextrin inclusion complex is stereoselective. The overall release of the water soluble propranolol hydrochloride from HPMC matrix showed a dependence on (i) diffusion of water, a nonstereoselective process, through the matrix and thereby hydrating it; (ii) diffusion of the enantiomers of the drug through the hydrated chiral matrix, presumably a stereoselective process; and (iii) erosion of the hydrated matrix, a nonstereoselective process. A time plot of the mean ratio (S:R) of the cumulative precentage of *(R)*- and *(S)*- propranolol hydrochloride enantiomers released from HPMC matrices showing stereoselectivity in dissolution is presented in Fig. 5.1. The dissolution results of this study have been analyzed using equation (1) to estimate the values of n. For *(R)*-propranolol, n = 0.767 while for *(S)*-propranolol, n = 0.777 thereby indicating the release to be controlled by both diffusion of the drug in the hydrated matrix and erosion of the gel matrix itself.

In an effort to investigate the effect of polymer viscosity in a matrix system on drug release, 25 matrices of varying viscosity grades of HPMC (Metolose) at different HPMC concentrations and propranolol hydrochloride were prepared[75]. The drug and HPMC were thoroughly mixed in a mixing bag for 10 min. A weighed amount of the mixture was fed manually into the die of a single punch-tableting machine (Manesty-E2, England) to produce a matrix of 300 mg and a porosity of 0.15 using flat-surface punches of 9.5 mm diameter. The dissolution experiments were carried out at 37°C in 1000 ml distilled water at 100 rpm. Matrices containing 5, 10, 25, 50 and 75% (w/w) of HPMC were prepared. Matrices formed using 5% of HPMC retarded the drug release only marginally. More than 60% of the drug was released within 30 min and 80% was released in 1 h. However, a complete drug release was obtained within 4 h. The drug release data were analyzed using *Higuchi* equation:

$$\frac{W_t}{\sqrt{t}} = A\left[DS\left(2\frac{W_0}{v} - S\right)\right]^{1/2} \qquad (15)$$

where W_t is the amount of drug released in time t, A is effective diffusive area, W_0 is the initial amount of the drug present in the matrix, v is effective volume of the hydrated matrix, D is diffusivity, S is solubility of the drug in the polymer matrix. These findings suggested that the diffusion layer model suggested by *Ford et al*[22] is operative. The results indicated that an increase in viscosity in the high molar mass grades of HPMC promoted water entry, whereas the reverse effect was observed with the lower molar mass grades. In addition, the solution viscosity and gel thickness vary directly with the viscosity grade of HPMC. It was concluded that solution viscosity can be varied with the thickness of HPMC forming the gel layer as well as its viscosity grade.

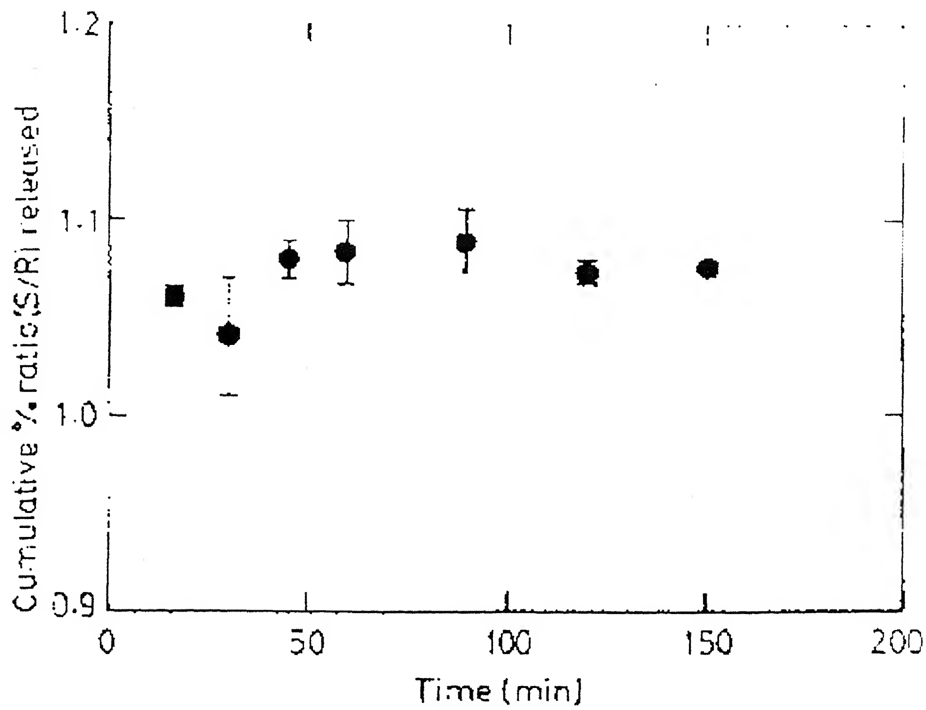


Fig.5.1. Mean cumulative % ratio (S/R) vs. the time of propanolol hydrochloride enantiomers released from HPMC matrices in the four experiments showing stereoselectivity in dissolution. The vertical bars show standard deviations for four observations.

5.1.4.ii. Diltiazem hydrochloride

Dilitazem hydrochloride is a calcium channel blocker and is effective in angina. Its ER formulation is also used for treatment of hypertension. Multi-layered hydrophilic matrix tablets have been developed as ER devices for diltiazem hydrochloride with HPMC matrices and their effectiveness, reproducibility, and technological properties have been studied *in vitro*[4]. The development of a formulation that is able to reproduce an inert film coating performances either to delay the core hydration rate or to prevent drug diffusion from protected surfaces was carried out by two different approaches. The first was based on the use of an insoluble inert polymer (ethyl cellulose) formulated for tableting procedure (barrier E). The second was based on hydrophilic swellable HPMC polymer that was also used in the active core

formulation. A model formulation containing diltiazem hydrochloride was designed as a hydrophilic, slowly swellable, but almost non-erodible heterogeneous matrix. The active core compositions are given in Table 5.5.

Table 5.5. Active core % compositions[4].

Active core	Composition%
Diltiazem hydrochloride, USP	46.87
HPMC, USP (100,000 cPs)	36.46
Mannitol, USP	10.41
Ethyl cellulose, NF (20 cPs)	4.69
Magnesium stearate, NF	1.04
Colloidal silicon dioxide, NF	0.52

Matrix tablets were partially coated on various sides with an inert impermeable film. The coating was applied manually on the tablet base or on the sidewall to have different coating combinations. These combinations are shown schematically in Fig. 5.2. The release patterns of the model formulation uncoated matrix (type-0) and of the four coating designs (types 1, 2, 3 and 4) are presented in Fig. 5.3. A progressive shifting of the release kinetics towards constant drug release was achieved by increasing the extent of surface area coated with the barrier. In order to verify the barrier layer efficiency in the control of drug release profile, batches of double-layer (type 1) and three-layer systems (type 2) were prepared[76] by applying in one or both tablet bases or the film coat F (manually by casting) or 30 mg of the barrier layers C (by compression) as shown in Fig. 5.4. Dissolution experiments were performed on the uncoated devices, on the film-coated devices (1F and 2F), and on the tablets coated by compression with the barriers (1C and 2C). The percent amount of drug released at various time intervals was determined (at 100 rpm in 900 ml distilled water, 37°C) spectrophotometrically at 236 nm and these results are compared in Fig. 5.5. It was found that the presence of coatings reduced the drug release rate proceeding from the 'two-' to the 'three-layer' systems. With the

swellable polymeric barriers (1C and 2C) compared with the film (1F and 2F), this effect was more pronounced. In case of 'three-layer' tablets, the drug release rates decreased further, approaching zero-order kinetics. The influence of compression force on the release patterns and on the crushing strengths was also evaluated on these systems.

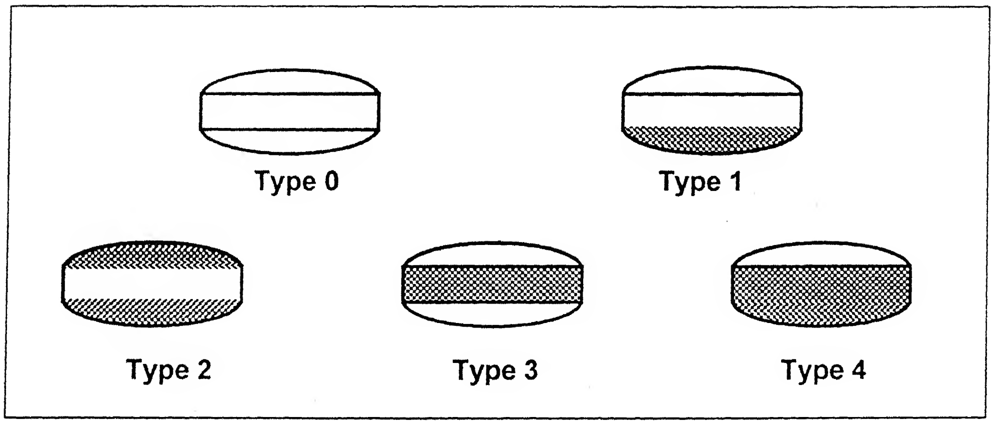


Fig.5.2. Schematic drawing of the four coating patterns studied and the uncoated matrix tablet (Type 0).

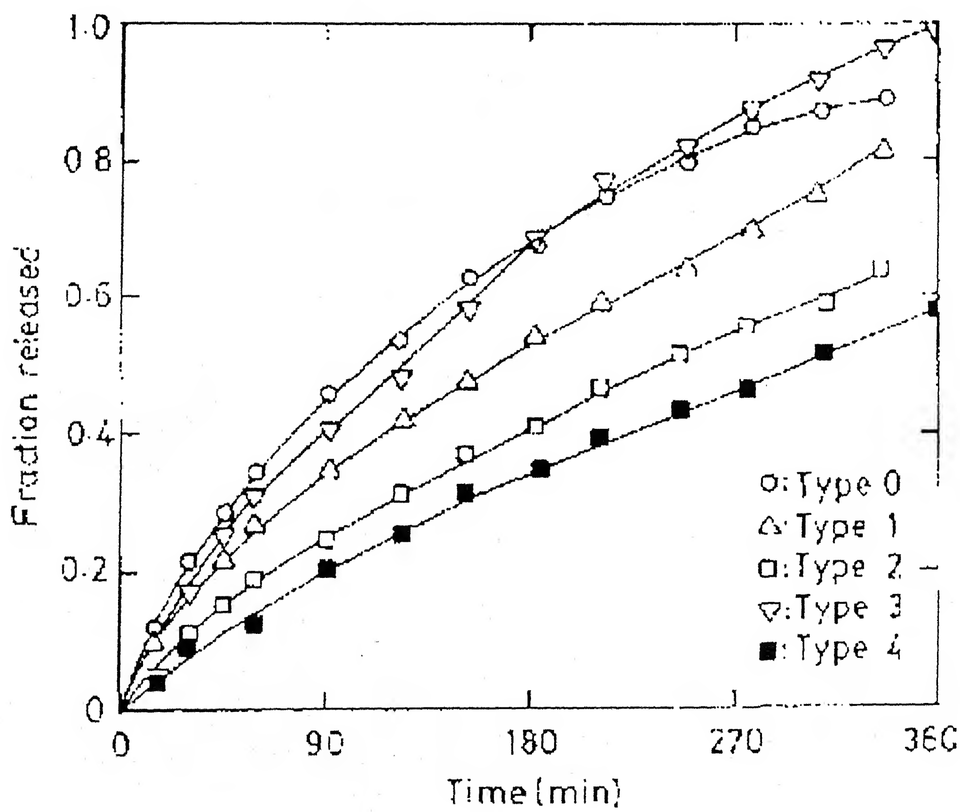


Fig.5.3. Release profiles of the uncoated matrix (type 0) and the four-coated patterns examined and exponent n calculated from equation (1).

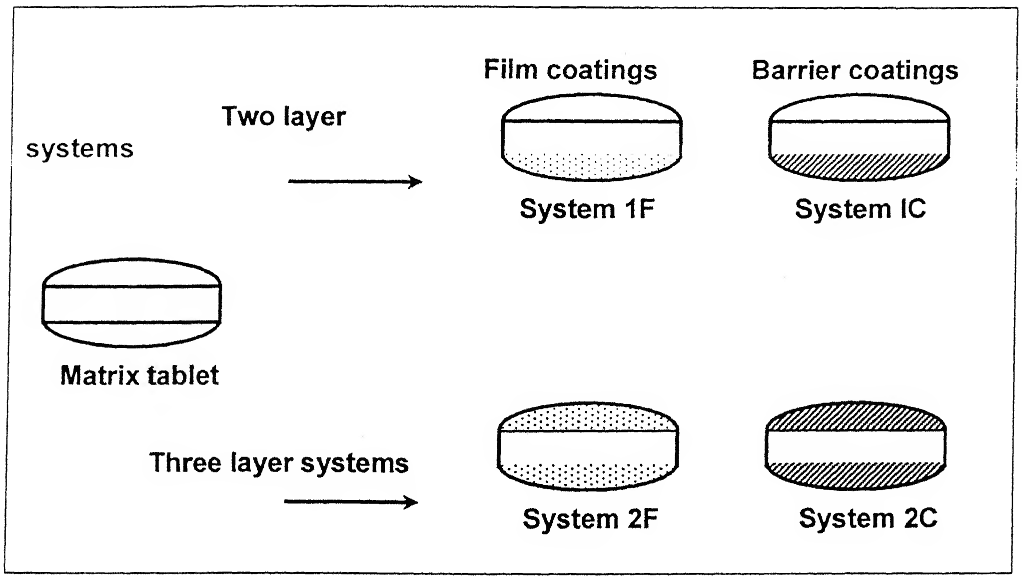


Fig. 5.4. Schematic drawing of the film- or barrier-coated systems.

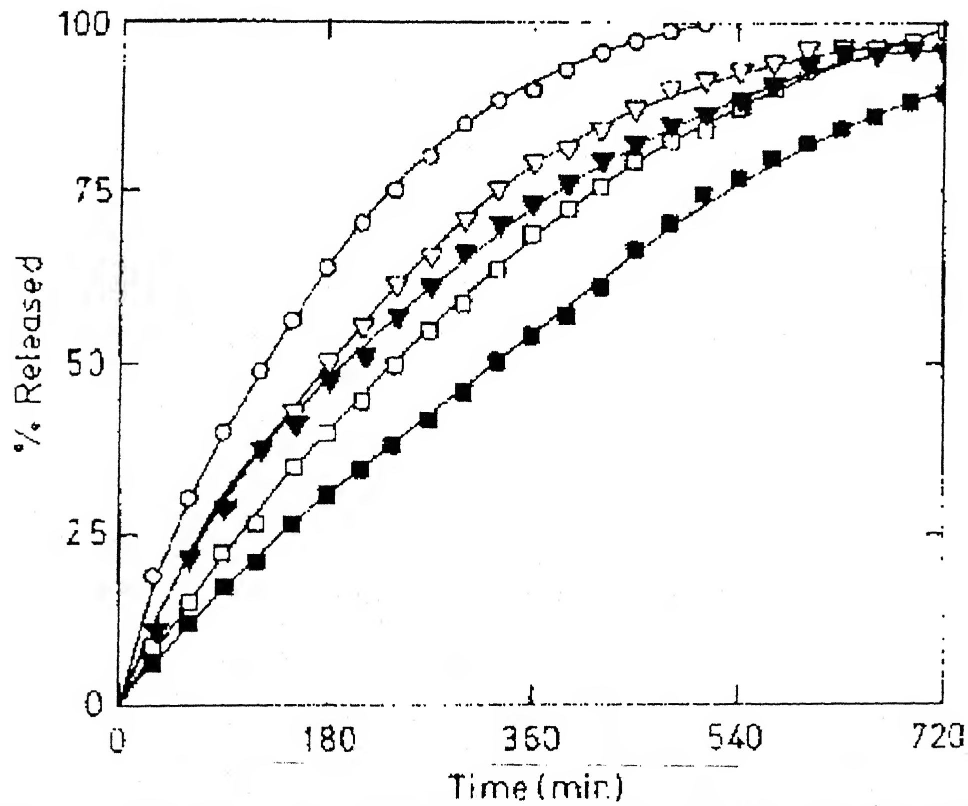


Fig.5.5. Comparison of the percentage of drug release vs. the time of uncoated matrix tablets (O); two-layered-coated systems, 1F (▼) and IC (Δ); and three-layer-coated systems, type 2F(■) & 2C(□).

Swellable matrix systems with impermeable coatings that partially cover the matrix have been prepared and the ER of diltiazem hydrochloride from the plain matrix systems (plain matrix), matrices coated on one face (type 1) and matrices coated on two faces (type 2) was also studied[76]. The release patterns of the three systems were significantly different. The morphological changes in the three types of systems were observed by photography. Drug release was markedly reduced because of the coating of the matrix bases. The t_{50} obtained with the flow-through apparatus for the three identical matrices without coating, with coating on one face and with coating on two faces were 108, 160 and 234 min, respectively. The kinetics of drug release was evaluated by equation (1). From the values of n obtained, it was found that the kinetics of plain matrix follows the anomalous behavior, which tends to approach a constant release with increasing number of coatings applied. The differences in the release patterns are displayed in Fig. 5.6. The extension of releasing surface during swelling increased more slowly as the area of the coating applied increased. Because coating changed the dimensionality of the matrix swelling, the kinetics of matrix relaxation was also changed. The drug release kinetics followed the kinetics of matrix relaxation, expressed by the external releasing surface increase of the matrix. It was concluded that the application of an impermeable partial coating to a swellable matrix reduces the amount of drug released by reducing the available releasing area of the system.

The release mechanisms of the SR swellable systems prepared by the coating methods suggested by *Conte et al*[4] have been further studied[77] using diltiazem hydrochloride as the drug, mannitol FO IX as the filler and HPMC as the swellable polymer. The variations in matrix relaxation and drug diffusion rates were quantified by measuring the surface area exposed during the matrix swelling and the drug release as a function of impermeable coating coverage and location. Compressed discs were coated with an impermeable coating in order to prepare the five types

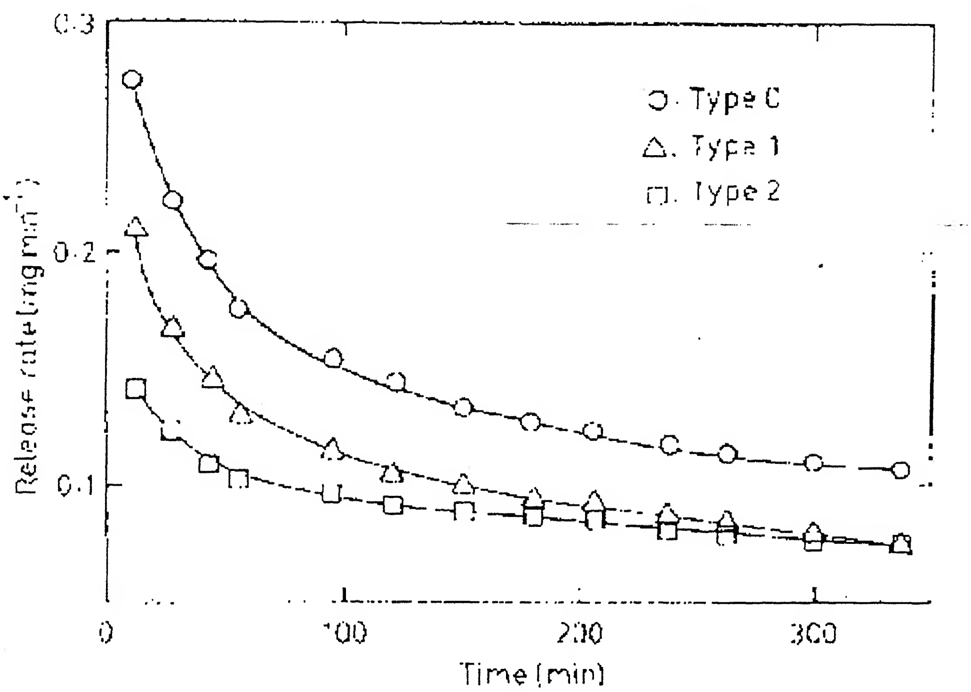


Fig. 5.6. Instantaneous release rates of the three types measured from the flow through drug release.

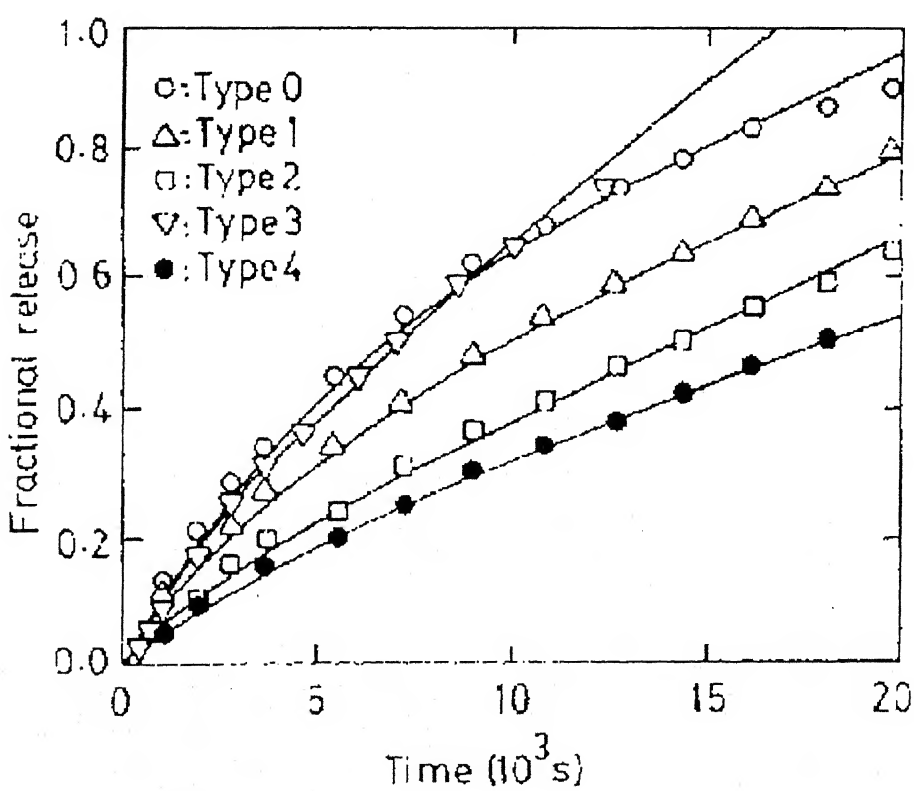


Fig. 5.7. Fractional release of diltiazem hydrochloride from five types prepared by coating vs. time.

illustrated in Fig. 5.2 with the same codes as: type 1, type 2, type 3 and type 4, as given[76]. The diffusion coefficient of diltiazem hydrochloride in the swollen matrices measured in a standard diffusion cell was found to be 6.2 x 10^{-6} cm^2/s. The release data of these five types are presented in Fig. 5.6. The release mechanism in all the types [(fitted by equation (1)] was found to follow the anomalous transport because the values of n varied between 0.64 to 0.84, thus showing an effect of coating on the release rates of the drug. The results of analysis of equation (1) are given in Table 5.6. The fractional release data of diltiazem hydrochloride for five different coatings are presented in Fig. 5.7 while Fig. 5.8 displays the dependence of diltiazem hydrochloride flux vs. time for the same formulations.

The release results were further correlated by the Peppas and Sahlin model[78]. Four different types of matrices that were partially coated on various sides were investigated to study the role of swelling behavior on the drug release, taking into account the three-dimensional nature of swelling. The dependence of release kinetics on the matrix surface area was investigated. A new dimensionless swelling area number was defined to evaluate the significance of the relative rate of matrix swelling variation and drug diffusivity. The systems studied were produced by a partial covering of the release area of tablets by an impermeable coating.

Table 5.6. Release data of different systems[77].

System Type	Kinetic constant $K \times 10^4/s^{-n}$	Diffusional exponent *n*
Type-0	19.0	0.66
Type-1	14.0	0.64
Type-2	2.6	0.79
Type-3	4.2	0.84
Type-4	2.9	0.76

5.1.3. Some Miscellaneous Cardiovascular Drugs

Verapamil, a calcium channel blocker, is widely used for the treatment of hypertension, supraventricular arrhythmias, and angina pectoris. It is well absorbed after oral administration, but has only about 25% bioavailability and is also classified as a highly variable drug[79]. Novel floatable and zero-order release formulations of verapamil using asymmetric configuration delivery systems containing 20% of HPMC K4M polymer along with other ingredients have been prepare[80]. The amount of verapamil released was measured by spectrophotometry at 230nm. These results showed that the gastric retention time of the delivery system was prolonged,

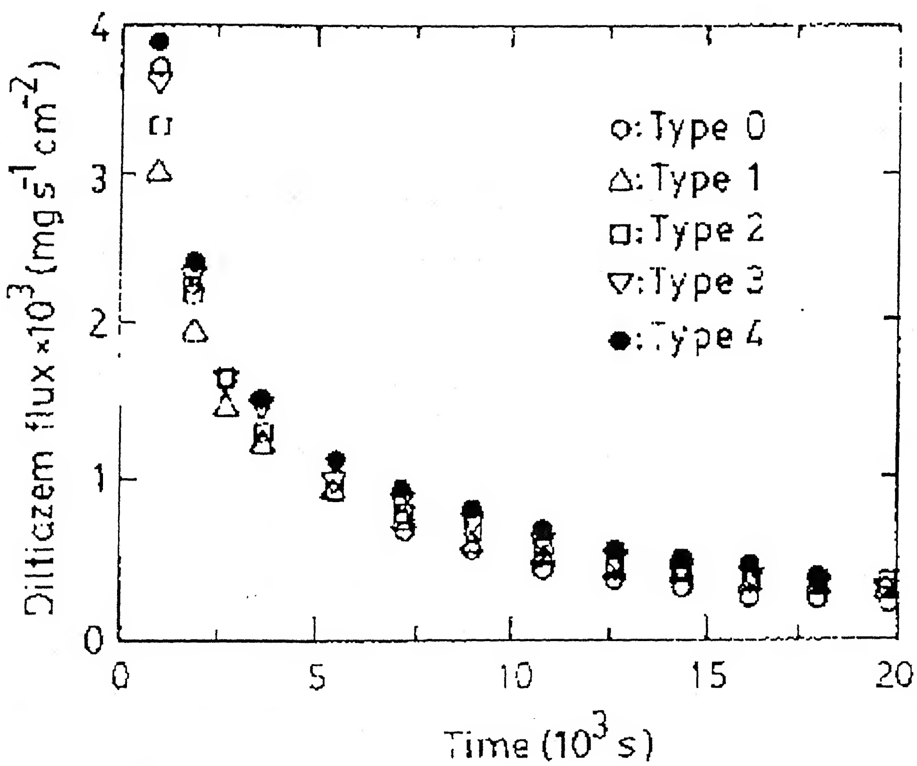


Fig. 5.8. Diltiazem hydrochloride flux vs. time for the five coating types prepared.

Improving the bioavailability of verapamil. The mechanism of release of verapamil hydrochloride and dyphyllline from coated swellable minimatrices was studied[81] by comparing the release kinetics of the systems based on the inert or swellable cores

and by measuring the permeability of the isolated membranes whose composition was identical to that of coating. The drug, polymers and filler mixtures were granulated by wetting with a 5% *iso*-propanol solution of Eudragit® RS. The mixtures were forced through a 710 μm screen and dried at 35°C. The granules were lubricated with a 0.5% magnesium stearate and tableted in a single punch at a punch pressure of 110 MPa. The core composition of the swellable (formulae a and b) and inert (formulae c and d) systems are given in Table 5.7.

The cores were coated in a rotating pan with 6% w/v of *iso*-propanol solution of a mixture composed of Eudragit® RS (58%), Eudragit® RL (15%), Eudragit® E (25%), and 2% of castor oil. The dissolution tests were performed in a simulated gastric fluid without enzymes using paddle apparatus (1000 ml, 37 ^{O}C, 100 rpm). Verampil HCl and dyphylline were assayed spectrophotometrically at 278 and 273 nm respectively. Polymer film average thicknesses of 100 μm were used for permeability studies using, a Sartorius Apparatus (Model SM 16750). The release data were fitted to equation (12). It was found that for the coated matrices the release kinetics shifts towards a constant release depending on the increase in film thickness. Furthermore, the observed value of n = 0.5 indicated the transport to be of *Fickian* type. The ER in this study was ascribed to a physical restriction exerted by the film on core swelling. It was concluded that the film coating was not the rate-limiting step in the drug release from swellable minimatrices.

Table 5.7. Percent core composition[81].

Formulae	**a**	**b**	**c**	**d**
Verampil HCl	30	-	30	-
Dyphylline	-	30	-	30
Methocel® K 15M	20	20	-	-
Ethocel®	-	-	50	50
Talc	50	50	20	20

Dipyridamole is an antithrombotic and vascodilator, used in the long-term therapy of chronic angina pectoris with usual dosages of 50 mg three times daily[82]. It is characterized by a dissolution rate, which is very high at acidic pH, but very low at neutral/basic pH and to date, its very few ER formulations are available[83]. In an effort to study the extended release hydrophilic matrix containing dipyridamole by loading the swellable crosslinked NaCMC polymer with dipyridamole as drug and enteric polymer (cellulose acetate phthalate or cellulose acetate trimellitate), *Giunchedi et al*[84] devised an oral extended release formulation. The drug release was studied *in vitro*. Tablet formulations containing hydrophilic matrices were prepared by mixing the granules with HPMC and then tableting the resulting mixture to examine the drug release rate. Here, the dipyridamole SR formulations were prepared by the two methods: (i) three-component modified release granules made up of swellable polymer loaded with dipyridamole and an enteric polymer - the drug/enteric polymer/swellable polymer weight ratio used was 1:2:1 and (ii) extended release formulations made up of hydrophilic matrices, resulting from tableting mixtures of the modified release granules with the gelling HPMC polymer. The compositions of the modified release granules and of the extended release granules are given respectively, in Tables 5.8 and 5.9.

Dissolution experiments were carried out at 37°C and 100 rpm by the following procedures: (i) at constant pH, 1000 ml of gastric simulated fluid (pH 1.2) and 1000 ml of intestinal simulated fluid (pH 7.5), both without enzymes; (ii) with pH variation: 750 ml of 0.1N HCl (pH 1.0) from 0 to 2 h of the test and then addition of 250 ml of 0.2M tribasic sodium phosphate solution to give a pH of 6.8 in a total volume of 1000 ml. The *in vitro* tests at constant pH were performed on samples of 100 mg of dipyridamole in the powder form, samples of the modified release granules containing the equivalent of 100 mg, and the tablets. The tests with pH variations

were performed only on the tablets. Due to variations in the UV absorbance of the drug in different dissolution media, dipyridamole was determined spectrophotometrically at 283 nm for the tests in gastric medium or in 0.1N HCl and at 294 nm for the tests carried out in intestinal medium or in the final phosphate buffer of pH 6.8. In fact, the major element determining the duration of the drug release was found to depend on composition of the matrices rather than the pH of the dissolution medium.

Table 5.8. Compositions of the modified release granules[84].

Release system	% DIP	% CAT	% CAP	% CM-XL
DIPCAT	25	50	—	25
DIPCAP	25	—	50	25
DIP - dipyridamole; CAT - cellulose acetate trimellitate; CAP - cellulose acetate phthalate; CM-XL - crosslinked Na CMC.				

Table 5.9. Composition of the extended release matrices[84].

Matrix (Tablet)	DIPCAT [DIPCAP] (%)	Methocel K4M	Mannitol (%)
T1 (P_1)	80	20	—
T2 (P_2)	75	20	5
T3 (P_3)	75	15	10

Thus, the highest content of HPMC (T1 and P1) was characterized by the slowest release rates (at least 24 h of drug release), those containing 5% mannitol (T2 and P2) were slightly faster (~20 h of release), while 10% mannitol in the matrices (T3 and P3) did not give efficient drug release (i.e., about 70% dissolution of the drug only after 3-4 h), with the exception of P3 tablets in the intestinal fluid (about 85% dissolution of the drug after 18 h). Thus, it was concluded that the tests of modified release granules in simulated gastric fluid showed a modulation of the high

dissolution rate of dipyridamole at acidic pH and a very marked improvement in drug dissolution in the intestinal fluid. Studies of the tablets performed at constant pH and with pH variation showed that the matrices were capable of providing extended drug release in acidic medium and that they moderated the dissolution behavior of dipyridamole tablets under different physiological pH values.

Nifedipine is a calcium channel blocker used in the treatment of hypertensions, angina, and *Raynaud's* phenomenon. In addition to different polymeric forms, it can also exist in the glassy state. Since it is poorly water-soluble (6.2 mg/l at 26.5 ^{O}C), its bioavailability is expected to depend on the dissolution rate. Solvent evaporation and spraying methods were used[85] to load nifedipine onto the surface of a NaCMC to achieve an improvement in the dissolution rate. The addition of excipients for further improvement in dissolution and better surface distribution was discussed. The dissolution rate was not strictly dependent on drug crystallinity, but was more related to the water interaction properties of NaCMC. In another study[86], the bioequivalence in five human volunteers and the pharmacokinetic parameters of an ER hydrophilic tablets of nifedipine prepared with HPMC as a swellable polymer were investigated. The results indicated that the hydrophilic tablets were useful as an ER formulation for the long-term treatment of hypertension.

The significance of factors such as drug solubility, polymer molecular weight, drug loading, compression force, and hydrodynamic conditions for the SR of nifedipine and diltiazem hydrochloride with solubilities of <0.001%, <0.1%, <1%, and <50%, respectively[87]. Changes in the pectin/HPMC ratios, the HPMC molecular weight, and hydrodynamic conditions had a significant influence on the release rate and release duration. It was further shown that the hydrodynamic stress and intensity of fluid flow caused greater attrition at the swollen periphery and were responsible for the dramatic increase in release rate. This observation confirmed that the mechanism of

drug release from a swellable system is erosion-dependent. The influence of the polymer molecular weight and drug solubility on the release kinetics and the potential of the delivery system were discussed.

A transdermal delivery system (TDS) was developed for the SR of nifedipine[88]. The physicochemical properties influenced percutaneous absorption like solubility and partition coefficient, thereby, confirming the drug's potential for the development of a SR formulation. However, these studies when performed for permeation through hairless mouse skin from a range of hydrophilic and hydrophobic donor vehicles indicated inadequate penetration. It was concluded that 1% sodium lauryl sulfate and 20% propylene glycol in a Na CMC (3%) gel base failed to increase the drug flux to an acceptable level. These results suggested that the development of a TDS for the chemically unmodified drug in humans is likely to be unsuccessful.

In continuation of their earlier studies by *Skoug et al*[89, 90] on HPMC-based SR tablets of adinazolam mesylate and alphrazolam, further efforts were made[7] to predict the relative changes in ER rates as a function of the formulation composition for HPMC-based ER tablets of adinazolam mesylate and alphrazolam using a mathematical model based on Higuchi equation[54]. The diffusional release of the soluble drugs from the polymeric matrices and concentration dependence of adinazolam diffusivity in dilute HPMC gels and their solutions were studied. Reasonable correlations were obtained between the experimental drug release rate ratios and the predicted drug release ratios for the ER of adinazolam mesylate and low-dose (0.5 mg) ER alphrazolam tablets. These results were found to be in agreement with the previous findings of the release mechanisms of these formulations.

The release mechanism from tablet matrices prepared with either of the two grades of HPMC polymers and panadiplon (U-78875) as a model drug with poor aqueous

solubility was investigated to define the conditions for selecting the appropriate polymers for ER formulation[9]. The viscosity of HPMC polymers, being related to molar mass, showed a great influence on the erosion rate of the matrix tablet. Use of a low viscosity grade HPMC was recommended for drugs that are poorly water-soluble and the release rates of the poorly soluble drugs could be controlled by the rate of tablet erosion. Tablet erosion rate could also be adjusted by the choice of viscosity grade of HPMC. The ability of ER tablet matrix systems containing HPMC to physically withstand the mechanical stresses involved in a reworking procedure was evaluated[16]. The influence of the nature of the polymer, the rework procedure, powder re-blending levels, and the compression characteristics were also been studied using chloropheniramine maleate, medizine dihydrochloride, and ascorbic acid.

The effects of polymer hydration rate, polymer concentration, and interactions of drug/polymer/excipients on the stability and release profiles of xanthinol niacinate (xantinolium nicotinate) from hydrophilic matrix tablets have been investigated[17] using different HPMC grades (Methocel K4M CR, K15M CR, E4M CR and E10M CR). The mechanical strength, average weight and mass variability, disintegration and dissolution of the drug were determined. The drug release was dependent on the type of polymer forming the matrix and its concentration. The dissolution rate ranged from 18 to 489 min and the total amount of the drug was released within 1 to 21 h. Methocel K4M CR in 20% concentration ensured the drug release by the zero order kinetics within 12 h.

A three-dimension (pH-time-solubility) solution test of SR release captopril tablets has been performed[91]. The results indicated that the effect of pH (ranging from 1.0 to 7.4) on the solubility of the drug was insignificant and that the solubility rate could be controlled by 20-45%, 45-70%, and 75% at 2,6, and 12 h, respectively. In addition,

the correlation between the solubility rate in vitro and the percentage absorption in vivo of this drug was analyzed with a good fit (r = 0.999).

5.1.4. CONCLUSIONS

The evolution of SR technology for the treatment of heart ailments is still at a primordial stage; nevertheless, some important practical applications have emerged, especially in the use of HPMC polymers. Further developments in this area seems limited only by the ingenuity shown by polymer chemists, pharmacologists and physicians involved in the SR research. However, those works in this field must astute enough to choose problems where the therapeutic benefits obtained via sustained drug delivery justify the expenditure of time, energy and investment involved in the developmental effort. For a successful development of a useful SR formulation of a cardiovascular drug, thorough knowledge is required not only of the physical and chemical properties of the drug and delivery systems, but also of the pathophysiology of the condition to be treated. This in turn, necessitates a close collaboration and communication between pharmaceutical chemist, polymer scientist, pharmocologist, physician and clinician. In some respects, the drug delivery research is more akin to engineering science than to the traditional biological/physiological research. Further research and developmental work on the SR of antihypertensive drugs through more number of other hydrogel based polymeric membranes has direct implications in this versatile and active field of research.

5.2. HYDROPHILIC MATRIX EXTENDED RELEASE TABLET

In the last two decades, hydrophilic matrices have become extremely popular in controlling the release of soluble drugs from solid dosage forms. Hydrophilic matrix consists of a mixture of one or more active ingredient(s) with one or more gel forming agent(s). The mixture is usually compressed into a tablet.

Swelling and matrix systems are differently identified by scientist. *Lee*[92] called them hydrogel matrices or polymer matrices exhibiting moving boundary. *Lippold*[93] adopted the physiochemical definition of hydrocolloid matrices. *Ford*[36] proposed hydrophilic matrix tablet while *Peppas* and *Korsmeyer*[95] used swelling controlled release systems.

5.2.1. Polymers

Polymres most widely used in preparation of hydrophilic systems include Hydroxypropylmethyl cellulose (HPMC), Hydropropyl cellulose (HPC), Hydroxyethyl cellulose (HEC), Xanthan gum, Sodium alginate, Poly(ethylene oxide), crosslinked homopolymers and copolymers of acrylic acid and sodium carboxymethylcellulose. They are usually supplied in micronized form because small particle size is critical for the rapid formation of gelatinous layer on the tablet surface.

5.2.2. Phenomea of Drug Release

First report on the used of compressed cellulose matrices for oral controlled release dosage form appeared in 1962[96]. *Higuchi*[97] in 1963 was first to present a detailed mathematical analysis of sustained release preparations. *Bamba et al*[98], in 1979 further developed the mechanisms of release from matrix systems that swell at the tablet periphery to form a gel which acts as a barrier to drug diffusion. Later, from time to time, various formulation factors influencing the release of drugs from

compressed hydrophilic matrices, viz., viscosity of the polymer[21], ratio of polymer(s) to the drug[21,101], mixture of polymers[21,99-100], compression pressure[99,104-105] thickness of the tablet, tablet shape and added diluents[22], particle size of the drug[21,101], pH of the matrix[106,107], entrapped air in the tablets[52], surface area of the tablets, influence of the surfactants[109], molecular size of the drug[110], molecular geometry of the drug[111] and solubility of the drug have been studies by several workers and have been reviewed.

Most of the researchers working in the area of controlled drug delivery believe that, ideally drug must be released from the dosage form at a zero order rate. However, in hydrophilic swellable matrices and erosion matrices, drug release rate declined continuously in a manner that essentially follows the classical square root of the time relationship. *Rangarao* and *Baveja*[111] were first to suggest the use of both an ionic and non-ionic cellulose ethers as a solution to this formulation problem.

HPMC is one of the most widely cellulose ether for producing matrix formulation[99-100,112-120]. The release of water-soluble drugs through uncross-linked HPMC occurs by a combination of diffusion and dissolution of the matrix itself following hydration[121]. Diffusion, however may not be significant to release of hydrophobic drugs. In general, drug release from HPMC matrix can be modified by various formulation factors, such as type of polymer, polymer concentration, drug particle size and the presence of additives[22,101,109,122-123]. *Ford et al*[22,101] investigated the influence of these formulation factors on drug release from HPMC matrix tablets. Analyzing a typical example of the release of water-soluble drugs from HPMC matrix tablets, drug release of up to 90% of the total drug fits the *Higuchi* equation. This indicated that erosion of the HPMC does not contribute to the release of water-soluble drugs[21,101,127]. Varying the polymer concentration is most efficient in controlling the drug release kinetics. Increasing the polymer concentration reduces the drug release rates.

The addition of a hydrophobic lubricant, such as magnesium stearate, stearic acid or cetyl alcohol, did not affect the release of highly water-soluble drug[21]. *Fore et al* have used different grades of HPMC (K100, the lowest viscosity grade amongst K4M, K15M and K100M) to study the effects of some formulation variables like drug particle size, compaction pressure, absence or presence of magnesium stearate, on the release rate of Promethazine hydrochloride from tablet matrices. Changing the size range of the drug from 45-65µm to 500-700µm produced only 12% increase in the drug release rate; possibly due to the drug particle size of the drug controlling the release rate from HPMC matrices by altering the matrix tortuosity.

5.2.3. Effect of Compressional Pressure

Variation in the compaction pressure or absence of 0.75% magnesium stearate did not appear to affect release rate[21].

5.2.4. Effect of Surfactants

Daly et al[100], felt that addition of anionic surfactants like sodium dodecylsulphate (NaDS) may modify release from HPMC matrices by binding to the polymer and increasing the viscosity. More simple molecules, for example insoluble diluents such as tribasic calcium phosphate or water-soluble diluents such as lactose may modify release rates. *Lapidus* and *Lordi*[105], showed that addition of lactose increased the release rate of Chlorpheniramine more than the equivalent amount of calcium phosphate, due to the former reducing the tortuosity of the diffusion pattern of the drug. *Feely* and *Davis*[109] in another set of studies, studied the ability of ionic surfactants to retard the release of drug from HPMC matrices and found that hydrocarbon chain length of the surfactant does not appear to influence the liberation rate of the drug but surfactant is effective when both, polymer and the drug are ionized and of opposite charge.

5.2.5. Effect of Viscosity

Polymer viscosity is known to modify the release rate and so it is of great importance in determining the final release properties of the dosage form. There has been a considerable interest in the relationship between bulk solution viscosity and the rate of dissolution of a wide range of materials[128-129]. *Huber* and *Christensen*[130], while investigating the release of a tracer (tartrazine) from two HPMC matrix tablets obtained that the higher viscosity grade HPMC released the tracer at a significantly lower rate than a lower viscosity grade. However, *Soloman et al*[131] indicated that the viscosity grade of HPMC only affected the lag time for potassium chloride diffusion to become quasi-stationary but did not affect the rate of release. *Harwood* and *Schwartz*[132], (1982) and *Nakona et al*[99] (1963) also found the release to be slower from the higher viscosity grades of HPMC. More recently, *Cheong et al*[133] have studies the relationship between polymer viscosity and drug release from HPMC polymers comes into contact with water, it absorbs water and swells to form a gel which serves as a binder to drug diffusion. The process of drug release from a HPMC- drug matrix, hydration and gelation of the polymer, dissolution of drug and diffusion of the dissolved drug through the resultant gel layer. Thus larger the amount, higher the viscosity grade of HPMC present in the matrix, more resistant the gel layer is to diffusion and greater the retardation of release of drug.

5.2.6. Method of Fabrication

In the purpose of designing a dosage form, which will utilize the matrix system, tablet matrix system is selected here. To formulate a matrix tablet, several workers have used direct compression[21,100,103,111,113,119,132-135] as a technique, which involves sieving, mixing, blending and compression of drug and polymer along with suitable excipient. Direct compression method is acceptable for the materials having good flow and compressibility and procedure is relatively simple.

Wet granulation is another technique for matrix formation[136-141]. Granules formed are dried, sieved, lubricate and then compressed to obtain tablets. Wet granulation can be performed on high shear mixer or fluid bed granulators[142]. Granulation is carried out using aqueous or hydroalcoholic binder.

In the present study, HPMC is used singly and the effect of different viscosity grades of HPMC and other polymer as a matrix material is evaluated. Both wet granulation and direct compression method have been tried.

Much attention today is paid to release mechanism from hydrophilic matrix. *Huber et al*[212] suggested that drug release was controlled both by diffusion of drug and attrition of gel layer. The first basic work on release kinetic was that of *Lapidus* and *Lordi*[143], who demonstrated the applicability of diffusion equation for a semi-infinite medium. *Peppas et al*[144-145] worked with swellable matrix model that accounts for volume change and solvent diffusion, solute release governed by solvent penetration velocity and were able to predict thickness of gel layer as function of time, rate of swelling and velocity of eroding front. More recently, *Colombo et al*[136] stressed importance of third front, the diffusion front, identified as the interface between the still undissolved drug and the drug in the gel layer. The existence of this layer was first reported by *Lee et al*[146-148]. Drug release is function of the dissolved drug layer that separates the diffusion front form the erosion front; the diffusion is present as long as the concentration of the undissolved drug exceeds its solubility in the swollen polymer matrix. *Paula Costa et al*[149] have recently published a comprehensive review on modeling and comparisons of dissolution data from solid dosage form. *Korsmeyer et al*[150] developed a simple model relating exponentially the drug release to the elapsed time. The model incorporates structural and geometric characteristic of drug release mechanism. This important value can be used to characterize the drug release

mechanism. The exponent value can be used to characterize the drug release mechanism whether it is *Fickian* or non-*Fickian* release.

5.3. EVALUATION OF EXTENDED RELEASE PELLETS AND TABLET FORMULATIONS

Although the state of science is such that *in vivo* testing is essential in the development and evaluation of dosage forms, assessment of the *in vitro* characteristics and quality of the product is also necessary. For solid controlled release dosage forms, drug release characterization is the most important amongst various *in vitro* tests because the *in vivo* absorption is determined by the release of kinetics of the dosage forms. A validated in vitro dissolution test can serve the purposes of

(a) Providing necessary quality and process control;

(b) Determining stability of the relevant release characteristics of the product and

(c) Facilitating certain regulatory determinations and judgments concerning minor formulation changes, change in site of manufacture, etc.

However, the dissolution rate of a specific dosage form is essentially an arbitrary parameter that may vary with the dissolution methodology, such as type of apparatus, medium, agitation, etc. Unless it is demonstrated that the *in vitro* release behavior reflects the *in vivo* performance in humans, the data can be of no relevant value in predicting or judging the clinical effectiveness of a drug product. Therefore, development of a dissolution testing method for controlled release formulations should have *in vivo* considerations[151]. For the in vitro tests to be predictive, it should be discriminative and correlated with the *in vivo* performance. For the *in vitro* test to be reliable, the *in vitro* specifications must be relevant to bioavailability variables and

to the critical manufacturing variables that might be expected during normal manufacturing procedures.

Many issues and challenges related to dissolution testing of controlled dosage forms have been addressed by regulatory authorities[152-154] and in a recent review by *Khan*[155]. After a prototype formulation with acceptable ranges of process and composition variables has been identified, test variables should be studied, which include variations in pH, effect of surfactants, agitation, ionic strength, etc. The key elements during the dissolution evaluation include

(a) Reproducibility of the method;

(b) Maintenance of sink conditions;

(c) Dissolution profile with a narrow limit on 1 hour specification to assure lack of dosage dumping; and

(d) At least 75% of drug release at the last sampling to assure to complete release.

Out of the seven reported USP dissolution methods and tests conditions (Table 5.10) recommended for determination of drug release from oral extended release dosage forms as follows.

1. USP Apparatus I (Basket method): preferred for tablets.
2. USP Apparatus II (Paddle method): preferred for tablets.
3. USP Apparatus III (Bio-Dis dissolution method, or modified disintegration): useful for bead type dosage forms.
4. USP Apparatus IV (Flow through cell method): for insoluble drugs.

It should be pointed out that none of the existing in vitro method can perfectly mimic the *in vivo* situation given the nature of the *g.i.t.* and factor that affects its activity, and various mechanisms employed to achieve controlled release. *In vivo* drug absorption from dosage forms is known to be dependent on many factors other than dissolution,

such as transit time; permeability; solubility; luminal contents; metabolism and chemical stability in the *g.i.t.* Nevertheless, dissolution is an essential and critical step, particularly for controlled release drug products. Even thought it is only one of the process involved in drug absorption. Therefore, the ability to predict *in vivo* absorption characteristics from dissolution data of a controlled release dosage form has become one of the current emphases in the development of controlled release products. Development of an *in vitro/in vivo correlation (IVIVC)* for this purpose has been extensively discussed and explored over the last decade[156-160]. The existence of workshops research, and publications led to the issuance of guidance on this topic by the FDA in 1997[156]. The guidance presented a comprehensive perspective on the methods of developing and validating an *IVIVC* and its applications in setting dissolution specifications and using in vitro tests as a surrogate for an in vivo bioequivalence study in certain regulatory submissions.

Tablets are evaluated using various physicochemical parameter tests including their size, shape, color, odor, weight variation, thickness, hardness, friability, content uniformity assay[161-163].

Table 5.10. Test conditions commonly used in *in vitro* dissolution testing for controlled release dosage forms.

Media	1. Buffers over the full range of physiological pH (1-1.5, 4-4.5, 6-6.5, 7-7.5 for topographical plot); 2. simulated gastric/ intestinal fluids, i.e., 1 hour acid plus pH 7.4 buffer from1 hour on; 3. solutions of gradient pH: 1.2, 2.1, 5.5, 6.5, 6.7, 7.4; 4. water and 5. in some cases, surfactant may be used in dissolution media.
Volume of media	Sufficient to maintain "sink" conditions; the entire dose should dissolve in < 33% of the dissolution media.
Mixing	Different agitation rates including the standard conditions. Apparatus II may be more useful at higher rpm.
Sampling Schedule	1. At a minimum, three time points (1-2 hour, t_{50} & t_{80}. 2. Early sampling times for assurance against premature release:

	1, 2, 4 hours and every 2 hour thereafter, until 80% of the drug is released.
No. of units to be tested	12
Temperature	37 ± 0.5 ^{O}C

5.4. METOPROLOL TARTRATE

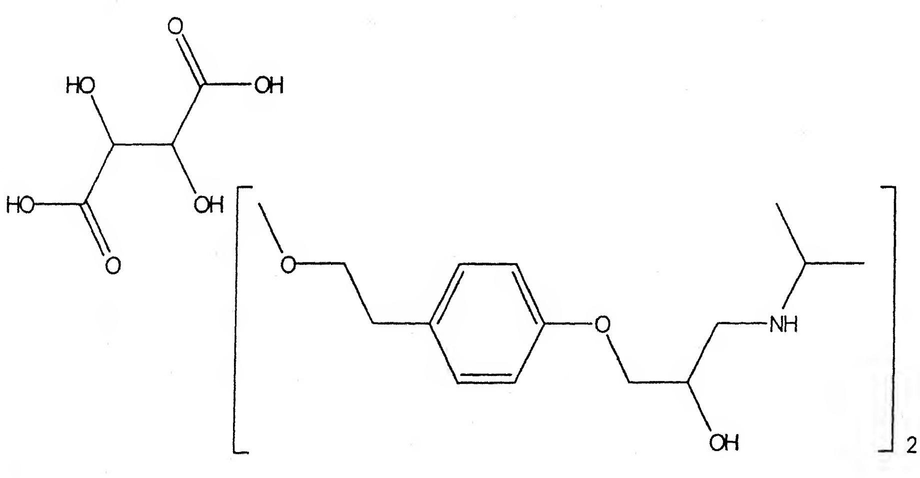
5.4.1 DESCRIPTION

5.4.1.i. Introduction

Metoprolol tartrate is a synthetic, selective β_1-adrenoceptor blocker lacking intrinsic sympathomimetic activity[164]. Its use is approved in Australia, Belgium, Canada, France, Germany Zokoslivakia, India, Ireland, Italy, Netherlands, Norway, South Africa, Spain, Sweden, Switzerland, UK, USA approved in India, US, UK, etc.[165]

5.4.1.ii. Chemical Formula, Name, Molecular Weight

$(C_{15}H_{25}NO_3)_2 . C_4H_6O_6$ MW 684.82



Metoprolol Tartrate

Metoprolol tartrate is a 2:1 salt consisting of a racemic mixture of optical isomers of the base and naturally occurring dextro-tartaric acid. The compound has been described by the following chemical names.

- 2-Propanol, 1-[4-(2-methoxyethyl) phenoxy (]-3-[(1-methyethyl) amino]-, [R-(R*, R*)]-2,3—dihydroxybutanedioate (2:1) (salt)
- (±)-1-(Isopropylamino)-3-[*p*-(2-methoxyethyl)-phenoxy]-2-propanol L-(+)-tartrate (2:1) (salt)
- 1-(Isopropylamino)-3-[*p*-(2-methoxyethyl)-phenoxy]-2-propanol (2:1) *dextro*-tartrate salt

5.4.1.iii. Appearance, Color, Odor

A white crystalline powder or colorless crystals[165], virtually odorless[166].

5.4.2. PHYSICAL PROPERTIES

5.4.2.i. Ultraviolet Absorption Spectrum:

The ultraviolet absorption wavelength (λ_{max}) and molar absorptivities (ε) of metoprolol tartrate in several solvents are listed in Table 5.11.

Table 5.11. Ultraviolet absorption wavelength (λ_{max}) and molar absorptivities (ε) for metoprolol tartrate.

Solvent	λ_{max} (nm)	$\varepsilon \times 10^{-3}$	Solvent	λ_{max} (nm)	$\varepsilon \times 10^{-3}$
0.1 HCl	221	19.5	Methanol	223	21.5
	274	2.83		276	3.11
	281 shoulder	2.31		282	2.62
Water	223	23.4	Chloroform	277	3.36
	274	3.60		283	2.86
	280 shoulder	2.94			
0.01N NaOH	223	24.0			
	274	3.66			
	280 shoulder	3.00			

5.4.2.ii. Infrared Absorption Spectrum

The infrared (IR) absorption spectral assignments[166] for metoprolol tartrate obtained as Nujol mull for major absorption bands are given in Table 5.12.

Table 5.12. Infrared absorption spectral assignment for metoprolol tartrate.

Wave number (cm^{-1})	Assignment(s)
3600-2300	$NH_2^{\bullet}$, -OH, Aliphatic and Aromatic CH
1580	Carboxylic Acid Salt
1580, 1515	Aromatic Ring
1250, 1015	Aromatic Ether
1180	Isopropyl Group
1100	Aliphatic Ether, Secondary Alcohol
820	1,4-Distributed Benzene

5.4.2.iii. Melting Range

Metoprolol tartrate melts over a 1-2 degree range between approximately 120-123^{o}C[166] when determined by USP method.

5.4.2.iv. Dissociation Constant

Dissociation constant (*pKa*) for secondary amine of metoprolol tartrate determined by potentiometric method are in the range of 8.9 to 9.5 (± 0.2) at 8 x 10^{-4} M in water at 25^{o}C[166]. The pKa values for tartaric acid are 2.93 and 4.23 at 25^{o}C[164].

5.4.2.v. Solubility

Metoprolol is moderately lipid soluble[167]. The approximate solubility of metoprolol tartrate in various solvents is given in Table 5.13 at 25^{o}C[166,168,169].

Table 5.13. Solubility of metoprolol tartrate in various solvents at 25 °C.

Solvent	Solubility (mg/ml)	Solvent	Solubility (mg/ml)
Water	Very soluble	Acetone	Slightly soluble
Methanol	Freely soluble	Acetonitrile	Sparingly soluble
Ethanol	Freely soluble	Hexane	Insoluble
Chloroform	Freely soluble	Ether	Insoluble
Dichloromethane	Soluble	----	---

5.4.2.vi. Hygroscopicity[166]

Metoprolol tartrate is a hygroscopic at high humidities. The water absorptions isotherm at 25°C indicates that the material rapidly absorbs water at relative humidities greater than 70% and conversely desorbs water as the relative humidity is decreased. No hydrate or change in crystal from has been observed.

5.4.2.vii. Distributive Ratio[166]

Distributive ration data, expressed as the organic phase concentration divided by the aqueous phase concentration, are summed up in Table 5.14.

Table 5.14. Metoprolol distribution ratio in difference organic to aqueous phases

Organic Phase	Aqueous Phase	Distribution Ratio
1-Octanol	0.067 M Phosphate Buffer, pH 7.4	0.587 ± 0.007
1-Octanol	0.067 M Phosphate Buffer, pH 7.4 with 0.9% NaCl	0.665 ± 0.008
Hexane	0.067 M Phosphate Buffer, pH 7.4	0.0040 ± 0.0005
Hexane	0.067 M Phosphate Buffer, pH 7.4 with 0.9% NaCl	0.0047 ± 0.0001
Chloroform	0.1 M NaOH	542 ± 16
Chloroform	0.1 M HCl	0.0040 ± 0.0003

5.4.3. STABILITY

5.4.3.i. Solid State Stability[166]

Metoprolol tartrate stored at room temperature and at 35°C for 5 years is physically and chemically stable. After storage at 50°C for up to 30 months, no degradation has

been observed – the only change has been that the material became slightly off-white; at lower temperatures and at shorter times intervals at 50°C, it has been completely unchanged in color. Under high humidity, the material is hygroscopic and rapidly absorbs water at relative humidities greater than 70%; however upon drying and reanalysis, the material is found to have retained its chemical and physical integrity.

5.4.3.ii. Solution Stability

No chemical change has been observed for solutions of metoprolol tartrate buffered at pH values of 4, 7 and 9, which have been stored at 60 °C for 10 days[166]. Drug solutions prepared in 0.1 N HCl, pH 7 phosphate buffer and 0.1 N NaOH, refluxed for 20 hours have shown no evidence of chemical change. Ampoules containing aqueous solution of drug in 1mg/mL and 0.9% NaCl have not shown any evidence of chemical change after storage for 77 months at room temperature and at 50°C[166]. A 0.4 mg/mL in 5% glucose or 0.9% NaCl was stable for 36 months when stored at 24°C in polyvinyl chloride bags[170].

5.4.4. HUMAN PHARMACODYNAMIC STUDIES

5.4.4.i. Effect on Heart Rate and Cardiac Output

Acute or chronic[172-173] administration of metoprolol to normal subjects or hypertensive patients results in a reduction in heart rate and cardiac output which appears to be related to the dose of the drug[174,175,176]. Stroke volume is unchanged[176,175]. A dose related reduction in exercise tachycardia after oral administration of 20, 50 and 100 mg or i.v. administration of 5, 10, 15 and 20 mg was noted by *Johnsson*[177]. For identical response, the relation between oral and intravenous doses was about 2.5:1 in comparison of the long-term haemodynamic effects of alprenolol (400 to 800 mg daily), atenolol (100 to 200 mg), timolol (10 to 20 mg) and metoprolol (50 to 300mg),

all drugs produced a comparable reduction in cardiac output but the fall in heart rate was most pronounced with atenolol and timolol[178].

5.4.4.ii. Effect on Blood Pressure

Single doses of metoprolol given orally or intravenously to normal subjects or hypertensive patients[171,177-178] rapidly lowered systolic blood pressure. Although diastolic pressure was not reduced by a single dose, it was significantly reduced by 150 to 450 daily for 3 to 4 weeks [180,172].

5.4.4.iii. β-Adrenoceptor Selectivity

5.4.4.iii.a. Effect on Haemodynamic Response to Sympathomimetic Agents

Adrenaline causes vasodilatation in muscle by activation of β_2-adrenoceptors. After a single i.v. dose of propranolol this vasodilating action is lost, and there is vasoconstriction, an increase in peripheral vascular resistance and a rise in blood pressure, presumably as a result of α-adrenoceptor stimulation. After a single i.v. dose of metoprolol, the vasodilating action of adrenaline (0.1 μgm/kg/min) is largely preserved[181,182]. The difference in interaction of the two β-adrenoceptor blocking drugs with adrenalin is interpretated as being the result of a much less pronounced effect of metoprolol on the adrenergic β_2-adrenoceptor compared with propranolol. Further evidence of the selectivity of metoprolol is illustrated by its minimal effect on lung function[183-187].

5.4.4.iii.b. Effect of Lung Function and Response to β_2-Adrenoceptor Stimulants

In asthmatic patients not experiencing an exacerbation of their asthma, single[183-184] or multiple oral[185] (50 to 100 mg) or single i. v. doses (0.12 mg/kg; 8 mg) of metoprolol[186-187] generally caused some reduction in basal FEV_1[183,185,186-187] FVC[187] and specific airways resistance[184]. This effect is less than that produced by equiactive β-blocking doses of propranolol. Unlike propranolol however, metoprolol does not significantly inhibit the branchodilatation induced by infused isoprenaline[183,186], or inhaled isoprenaline[185].

5.4.4.iv. Effect on Plasma Renin Activity

Metoprolol, given continuously or in single doses[188] reduces plasma renin activity (PRA) in hypertensive and in normal subjects. It may also reduce PRA in hypertensive patients previously treated with pindolol, practolol or oxyprenolol[189].

5.4.4.v. Metabolic Effects

5.4.4.v.a. Serum Glucose and Insulin Levels

It is thought that the adrenergic receptor, which modulates insulin secretion, may be a β_2-receptor[190], which might be affected to a lesser degree by a β_1-adrenoceptor selective blocking drug such as metoprolol than by a non-selective drug such as propranolol. *Newman*[191] reported that oral 100 mg metoprolol daily for 2 days delayed the return to normoglycaemia subsequent to insulin induced hypoglycaemia in 11 healthy fasting volunteers, whereas *Davidson et al*[192] found a normal response following insulin hypoglycaemia in 5 fasted volunteers given intravenous metoprolol 20 mg followed by an infusion of 6 mg per hour. In 9 hypertensive males treated with metoprolol 150 to 450 mg daily for 4 to 17 weeks[173] the return to normal blood glucose after insulin was not significant from that during placebo.

5.4.4.v.b. Plasma Lipids and Catecholamines

Although a significant rise in fasting triglycerides during metoprolol therapy has been reported by other investigators[189], and some have found no consistent changes[173,193].

5.4.5. PHARMACOKINETICS

Metoprolol is completely and rapidly absorbed after oral administration, is rapidly distributed to body tissue[165]. Plasma levels vary considerably between individuals, due probably to significant hepatic "first-pass elimination" which results in 50% of the administered oral dose reaching the systemic circulation[194]. Metoprolol is only slightly bound to human serum protein, namely albumin, which is reflected in its large volume of distribution[194]. The elimination half-life of Metoprolol is about 3 to 4 hours in most patients (range 2.5 to 7.5 h) and is independent of dose and duration of therapy[194]. The drug undergoes extensive biotransformation, and is excreted principally via the kidneys, only about 3% being excreted as the unchanged drug after oral administration and about 10% after intravenous administration[194]. The metabolites have no clinically important activity[194].

5.4.5.i. Absorption

Studies with oral and intravenous titrated Metoprolol indicated the drug is rapidly and completely absorbed[195-196]. Absorption appears to take place over a wide part of the intestine as radioactive doses given as ordinary or slow-release tablets of varying dissolution rates were completely recovered in the urine[195]. The estimated half-life of the absorption process is about 10 to 12 mins.[196] when metoprolol is administered as a weakly acidic solution. The rate of absorption is influenced by the dissolution rate of the oral preparation; peak plasma levels being attained 1.5 hour after ordinary tablets and 4 hour after slow release tablets. Plasma drug concentrations after i.v.

administration are higher than after an oral dose[177] and for an identical reduction in exercise heart rate the ratio between oral and i.v. doses is about 2.5[177].

About 40% of an oral dose of 5 mg metoprolol is available to the systemic circulation[195] although bioavailability increases to about 50% as the does is increases to 100 mg[177]. Plasma metoprolol levels vary between individuals and reach a peak at about 1.5 hour after oral administration[171; 195]. Ingestion of slow release tablets resulted in lower peak plasma levels of metoprolol, which were attained at about 4 hours. Although the mean area under the plasma concentration-time curve tended to be greater after the ordinary tablet the difference was not statistically significant[195].

Direct proportionality between plasma concentration and dose was obtained with intravenous doses above 10 mg and oral doses above 50 mg, but the ratio of the increase with dosage was higher at lower dosage levels. The increased bioavailability with increasing doses suggests the presence of some saturated disposition process of low capacity, especially after oral administration[177].

5.4.5.ii. Distribution

Metoprolol reaches concentrations in the erythrocytes ~20% higher than in plasma[196]. *Wood*[197] reported 267ng/mL metoprolol in the cerebrospinal fluid while the plasma concentration was 341 ng/mL, in the patient receiving 50 mg 3 times daily. Metoprolol has a high volume of distribution of 5.6 L/kg[196], which appears to be due mainly to the low degree of binding to human plasma proteins[198]. Metoprolol is only about 11% bound to human serum protein and appears to be bound solely to serum albumin[198-199]. In the same study, alprenolol was found to be 85% bound serum proteins. After oral administration of metoprolol, the plasma concentration curves do not show any clear-cut distribution phase (α-phase), but this phase is

clearly apparent after an intravenous dose[196] when the half-life of the distribution phase is about 12 mins.

5.4.5.iii. Metabolism and Excretion

Only ~3% of an oral dose and ~10% of an i.v. dose of metoprolol is recovered in the urine as unchanged drug[196]. Metoprolol is extensively metabolized in the liver. The hydroxy derivative of metoprolol, which accounts for ~10% of the urinary activity, has some β-adrenoceptor blocking activity, but this appears to be of no clinical significance[200]. Three main metabolites of metoprolol have been isolated and accounts for 85% of the total urinary excretion[201]. The main metabolite of metoprolol is an amino acid formed by O-demethylation and oxidation[201].

In healthy subjects, the renal clearance is 109 ml/min for the unchanged drug and 120 ml/min for the metabolites[196]. This value indicates that glomerular filtration mainly determines the excretion of metoprolol; although the existence of tubular secretion and reabsorption of about equal efficacy cannot be disregarded[196].

About 95% of an oral or intravenous dose of metoprolol is recovered in urine over a period of 72 hours. Whereas the elimination half-life of the total metabolites after oral administration is about 3 hours, that after an intravenous dose is ~ 5 hours, indicating that the route of administration might influence the metabolic pathways of metoprolol.

The elimination half-life of metoprolol in most patients is ~ 3 - 4 hours (range 2.5 to 7.5) and is independent of dose. The elimination half-life (3.7 hours) in elderly patients[202] is about the same as in younger health volunteers[177, 195]. However, the interindividual variation in peak plasma levels and elimination half-lives seemed to be more pronounced in the elderly patients. The finding that the elimination half-life is

almost the same after single doses or long-term administration indicated that metoprolol does not inhibit or induce its own metabolism[171]. However, there is some cumulation after a morning dose on long-term therapy being 45% higher than those after a single dose[171].

5.4.5.iv. Plasma Concentration and Clinical Effects

A significant relationship between the effect of metoprolol on heart rate and blood pressure during exercise and the logarithm of plasma drug concentration was reported by *Regardh et al*[195], but the relationship between plasma concentration and percentage reduction of systolic blood pressure in hypertensive patients was not significant in the study of *Bengtsson et al*[171]. Similarly, there was no correlation between the plasma concentration and the change in diastolic blood pressure after 4 months of therapy with metoprolol in 24 hypertensive patients' studies by A direct correlation between plasma metoprolol and reduction in exercise tachycardia in patients with angina pectoris was noted by *Keyrilainen* and *Uusitalo*[203].

5.4.5.v. Old Age

Several studies[204-206] indicate that age-related physiological changes have negligible effects on the pharamcokinetics of metoprolol.

5.4.5.vi. Pregnancy and breast-feeding

The clearance of metoprolol was increased four fold in 5 pregnant women during the last trimester, compared with that some months after delivery; this was probably due to enhanced hepatic metabolism in the pregnant women[207]. The disposition of metoprolol was investigated in newborn infants of mother treated with metoprolol 50 to 100 mg twice daily[208]. In 15 of the 17 neonates plasma-metoprolol concentrations increased in the first 2 to 5 hours of the post-natal period, then declined over the next

15 hours; 5 of these infants had no detectable metoprolol concentrations in the umbilical plasma. No infant demonstrated signs of beta blockade.

5.4.5.vii. Renal Impairment

A study of the pharmacokinetics of metoprolol and its renally excreted metobolite α-hydroxymetoprolol in normal and subjects with renal impairment[209]. Following a single dose of a sustained-release tablet of metoprolol, similar plasma-metoprolol concentrations and values for the area under the concentration/time curve were reported in both groups. Mean plasma concentrations of α-hydroxymetoprolol were increase two to three fold in subjects with renal impairment compared with normal subjects but such a rise was not considered likely to contribute to beta blokade.

5.4.6. THERAPEUTIC TRIALS

Controlled therapeutic trials in patients with angina pectoris or essential hypertension have shown metoprolol to be effective β-adrenoceptor blocking drug in these diseases.

5.4.6.i. Angina Pectoris

In patients with stable uncomplicated angina pectoris, metoprolol has shown to be more effective than placebo in reducing the frequency of anginal attacks and glyceryl trinitrate consumption and in increasing total work before onset of chest pain. In comparisons with propranolol, no significant differences could be detected between the two drugs[210-211], whilst in another study reported metoprolol was superior to propranolol[212]. Thus on the basis of present evidence it appears that metoprolol is an effective prophylactic drug in angina pectoris. Metoprolol has been shown to be superior to placebo in reducing the frequency of anginal attacks and consumption of

glyceryl trinitrate tablets as well as by the more reliable objective criteria of increasing total work on a cycle ergometer[180,203,210-211, 213-214].

An increase in dosage of metoprolol has not necessarily been reflected in an increase in clinical benefit[210]. It was reported that although doubling the dose of metoprolol from 12 to 240 mg daily was associated with an increase in plasma concentrations in all patients, clinical benefit was not uniform. However, there was tendency for clinical benefit to increase with the higher dose. An apparent lack of further clinical benefit upon increasing the daily dosage from 60 to 150 mg was reported by *Ekelund et al*[180], but the two placebo periods differed. Three patients experienced fewer anginal attacks during the placebo period between the low and high doses than during the period of active treatment with metoprolol 60 mg daily. On the basis of total work on a cycle ergometer, 3 patients responded adequately to 60 mg metoprolol daily but not to the 150 mg dose. These findings tend to support the need for individual dosage adjustment in patients with angina pectoris treated with a β-adrenoceptor blocking agent.

5.4.6.ii. Hypertension

5.4.6.ii.a. Comparison with Placebo

Double-blind studies comparing metoprolol with placebo in patients with mild to moderate essential hypertension[193,215-216] have shown that metoprolol is superior to placebo under controlled conditions, with statistically significant values.

5.4.6.ii.b. Comparison with other drugs

Metoprolol in fixed[217-219] or in individually titrated doses[192] has been shown to have antihypertensive activity similar to that of other β-adrenoceptor blocking drugs at equivalent β-blocking dosages, and to a α-methyldopa[220] and hydrochlorothiazine[221],

and superior to that of relatively low doses of trichlormethiazide[219]. No statistically significant difference between the antihypertensive activity of metoprolol 50 or 100 mg 3 times daily and 40 or 80 mg propranolol 3 times daily was found by *Bengtsson*[218]. However, *Bosman et al*[217] reported that 120 mg or 240 mg metoprolol daily was superior to propranolol in maintaining diastolic blood pressure. In comparison of metoprolol and thiazide diuretic, metoprolol 150 or 300 mg has been shown to be comparable with hydrochlorothiazide 50 mg to 100 mg[221] and superior to tirchlormethiazide 2 to 4 mg daily[219].

5.4.6.ii.c. Metoprolol Combined with Other Drugs

Metoprolol 150 or 300 mg daily alone or combined with hydrallazine 75 or 150 mg daily was reported by *Tuomilehto* and *Pakarinen*[222] to be effective in reducing sitting diastolic pressure to less than 95 mm Hg (9) or by more than 10% (6) in 15 or 17 patients who have failed to respond to previous antihypertensive therapy.

5.4.6.ii.d. Long-Term Treatment of Hypertension

Studies in which metoprolol alone in individually titrated doses of up to 450 mg daily has been given for periods of 3 months or more[172-173,223] have reported a significant fall in blood pressure, which has been maintained throughout the study. In a multicenter trial[223] involving 76 patients with previously untreated hypertension and 61 patients who were unsatisfactorily controlled by, or intolerant of previous therapy, metoprolol alone (75mg to 450 mg daily) led to a decrease in diastolic pressure to ≤95 mm Hg in 62% of the preciously untreated group and in 50% of those previously treated with other drugs. Most of the reduction in blood pressure was evident in the first month of treatment.

5.4.6.iii. Is the Efficacy of Metoprolol in Hypertension Influenced by Frequency of Administration?

Available literature suggests that once daily metoprolol is comparable in efficacy to a twice or thrice daily regimen in which the same total dose is given, reducing blood pressure in patients with mild to moderate hypertension.

Bengtsson[193] reduced the frequency of administration from thrice to twice daily in patients whose blood pressure has already controlled with a thrice-daily regimen. In this study the dosage as well as the frequency of administration was reduced (150 to 100 mg and 300 to 200 mg) but there was little difference in mean blood pressure after the change of the twice-daily regimen. Further data[224] suggest that in most patients studied, moderately elevated blood pressure can be satisfactorily controlled by once daily administration of metoprolol.

5.4.6.iv. Role Of Metoprolol In Hypertension

Studies with metoprolol indicate that it is as effective in lowering elevated blood pressure as any other β-adrenoceptor blocking drug given in a dose, which produces a similar reduction in exercise-induced increase in heart rate (i.e. at equi-β-adrenoceptor doses).

As metoprolol is a β_1-selective adrenoceptor-blocking drug, it may cause fewer tendencies to impair perihperal ciculation, heart failure and hypertensive reactions in states of catecholamine excess. "Caridoselectivity" lessens the risks of branchospasm, but does not impart any advantage with regard to its antinhpertensive action. Metoprolol may be better than non-selective β-adrenoceptor blocking drugs in the treatment of hypertension in patients who also experience Raynaud's phenomenon. β_1-Adrenoceptor selectivity may possibly also be an advantage in patients with diabetes mellitus, who are receiving insulin or oral hypoglycemic

agents, and those with angina or heart failure controlled by diuretics and digitalis drugs, but conclusive evidence for any advantage of β_1-selective agents in these conditions has yet to be demonstrated. Metoprolol is not suitable with partial agonist activity (e.g. patients at risk from A-V conduction impairment), but its lack of partial agonist activity may be of value in patents with muscle cramps[225], thyrotoxicosis[226], or in those who have a high-dose hypertensive response to pindolol[225]. As with other β-adrenoceptor blocking drugs, metoprolol is probably best given along with a diuretic and vasodilator in the more severe cases of hypertension[225].

5.4.7. SIDE EFFECTS

In therapeutic trials in patients with angina pectoris or hypertension, metoprolol has been well tolerated and any side effects reported have been moderate or mild and have generally not interfered with normal daily activities.

In studies that have employed questionnaires with lists of possible side effects, the frequency of adverse effects has been similar during placebo and metoprolol[180,203,211]. During a 6-month study in patients with angina pectoris, a greater proportion of side-effects (33%) interfered with normal daily activity during the first month than at 3 months (18%) and 6 months (17%). In this study, tiredness, insomnia, and gastric upset were the most frequently reported side-effects with metoprolol during long term treatment, although during subsequent double blind comparison with placebo in the same patients, the frequency of these and other side-effects on the check list were similar during both periods. Dizziness and tiredness have been the most frequently reported side effects in some other studies[193,215].

5.4.8. ADVERSE EFFECTS, TREATMENT AND PRECAUTION

5.4.8.i. Effects on bones and joints

Five cases of arthralgia associated with the use of metoprolol had been reported to the FDA[227]. A polymyalgia rheumatic-like syndrome has also been reported in one patient[228].

5.4.8.ii. Effects on the gastro-intestinal tract

Reports on retro-peritoneal fibrosis in patients who had been taking metoprolol and nifidipine[229] and of sclerosing peritonitis in a patient receiving metoprolol[230].

5.4.8.iii. Effects on hearing

Loss of hearing in a patient receiving metoprolol appeared to be dose related[231], hearing gradually improved over several months once the drug was withdrawn.

5.4.8.iv. Effects on lipid metabolism

Beta-blockers may increase serum triglyceride concentrations. For a report of acute pancreatitis provoked by severe hypertriglyceridaemia in patients taking atenolol and metoprolol[165].

5.4.8.v. Effects on the lever

Acute hepatitis associated with metoprolol as been reported in a 56-year-old woman[232]. The hepato-toxicity could not be explained by deficient oxidation of metoprolol; drug oxidation phenotyping showed she was an extensive metaboliser of debrisoquine and hence metoprolol.

5.4.8.vi. Carcinogenicity/Tumorigenicity

A 1-year study in dogs given upto 105 mg/kg per day orally, a 2-year study in rats upto 800 mg/kg per day orally, and a 21 month study in mice given upto 750 mg/kg per day orally found no evidence of carcinogenicity, although the incidence of small benign adenomas of the lung was higher in the treated female mice. A repeat of the 21-month study in mice found no increased incidence of any type of tumor[167].

5.4.8.vii. Mutagenicity

Metoprolol was not found to be muagenic in several tests including a dominant lethal study in mice, chromosome studies in somatic cells, a *Salmonella*/mammalian – mocrosome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei[167].

5.4.8.viii. Pregnancy/Reproduction

No adverse effect on fertility was observed n rats given upto 55.5 times the maximum human daily dose of 450 mg[167].

5.4.9. CONTRAINDICATIONS

Metoprolol should not be used if there is a risk of congestive heart failure, unless the patient is satisfactorily controlled with a diuretic and/or digitalis, and then given only cautiously; nor should it be used inpatients with right ventricular failure secondary to pulmonary hypertension. Significant cardiomegaly of any cause is an indication for considerable caution, as with other β-adrenoceptor blocking agents.

The drug should not be used in patients with sinus bradycardia (rates of less than 60 per minute) unless the patient is being paced, in patients with second or third degree atrioventricular block, in patients with cardiogenic shock.

If anaesthesia is required in patients taking metoprolol, the anaesthetic should be one that does not cause myocardial depression.

5.4.10. PRECAUTIONS

- As with other β-adrenoceptor blocking drugs, patients with mild or latent cardiac insufficiency should be given a diuretic and/or adequate dosed of digitalis prior to receiving metoprolol.
- Metoprolol may be administered with caution to patients with bronchitis and a tendency to wheezing, provided that branchodilator therapy with a β_2-adrenoceptro stimulant drug such as terbutaline, salbutamol etc is administered concomitantly. Although it is best to avoid any β-adrenoceptor blocking drug in asthma, some consider that low doses of metoprolol (up to 100 mg daily) may be given if it is thought essential in asthmatic patients, who must also be receiving optimum regular therapy with β_2-stimulant or institute combined oral and inhalation therapy in these patients.
- Metoprolol therapy must be reported to the anesthetist prior to general anaesthesia for surgery.
- Caution should be observed when treating when patients with unstable diabetes mellitus, as adjustment of the dose of the hypoglycemic agent may be necessary.

5.4.11. DOSAGE

5.4.11.i. Hypertension

Initially, 25 to 50 mg night and morning. This dose may be increased 100 to 200 mg twice daily depending on the response. Higher doses of up to about 400 mg daily may be given if required. There is some evidence that once daily administration may be effective in hypertension. Metoprolol may be given as part of a combined treatment regimen with a diuretic and /or a third drug (such as peripheral vasodilator)

where combined therapy is necessary to control blood pressure. Elderly patients may require lower maintenance dosages of metoprolol because of delayed metabolizing[233].

5.4.11.ii. Angina Pectoris

The usual dosage in angina pectoris is 50 mg 3 dimes daily. The 100 mg tablets may be administered thrice or twice daily to meet individual patients needs, although thrice daily administration of metoprolol is preferable during the initial period of treatment of angina pectoris.

5.4.12. OVERDOSAGE

A case of massive intoxication with metoprolol has been reported[234] in a 19-year-old male who ingested 10,000 mg (160 mgg/kg). The plasma level was 12,200 ng /gm plasma and 5,700 mg/Gm at 7 and 10 hours respectively. Initial treatment was gastric lavage, infusion of balanced electrolyte solution and sodium bicarbonate and control of blood pressure with metaraminol. After these measures, the patient was comfortable and without signs of cardiovascular depression 12 hours after admission.

5.4.13. OFFICIAL MONOGRAPHS FOR METOPROLOL

The USP 27[235] contains following monographs for metoprolol.

- Metoprolol fumarate, pp 1100-1101
- Metoprolol tartrate, pp 1101.
- Metoprolol tartrate Injection, pp 1101-1102.
- Metoprolol tartrate Tablets, pp 1102.
- Metoprolol tartrate - Hydrochlorothiazide tablets, 1102-1104.

5.4.14. METOPROLOL PREPARATIONS AVAILABLE IN INDIA

In Indian market, there are – brands of product, with – route of administration (oral, injectable) and of which – controlled /extended release products in different strengths, Details are given in Table 5.15[236-237].

Table 5.15. Marketed products of Metoprolol and in combinations available in India

Brand	Company	Packing	Strength
Single Drug Dosage Form			
Betaloc	AstraZenaca Pharma India Ltd., Bangalore.	10 Tablets	Metoprolol Tartrate 25 mg, 50 mg, 100 mg
		5 x 5 mL Ampoule	Metoprolol Tartrate 1 mg/mL
Lopressor	Novartis India Ltd., Mumbai.	10 Tablets	Metoprolol Tartrate 50 mg, 100 mg
Metocard	Torrent Pharm. Ltd., Ahmedabad.	10 Tablets	Metoprolol Tartrate 50 mg, 100 mg
Mepol	Taurus labs.	10 Tablets	Metoprolol Tartrate 50 mg
Metapro	Cardicare, Bangalore.	10 Tablets	Metoprolol Tartrate 50 mg
Metolar	Cipla Ltd., Mumbai.	10 Tablets	Metoprolol Tartrate 25 mg, 50 mg, 100 mg
		5 x 5 mL Ampoule	Metoprolol Tartrate 1 mg/mL
Metolar-XL	Cipla Ltd., Mumbai.	10 Capsules	Metoprolol Tartrate 12.5 mg, 25 mg, 50 mg, 100 mg
Composition Drug Dosage Form			
Betaloc-H	AstraZenaca Pharma India Ltd., Bangalore.	10 Tablets	Metoprolol tartrate 100 mg, hydrochlorothiazide 12.5 mg
Metolar-H	Cipla Ltd., Mumbai.	10 Tablets	Metoprolol tartrate 100 mg, hydrochlorothiazide 12.5 mg
Metozide	Torrent Pharm., Ltd., Ahmedabad.	10 Tablets	Metoprolol tartrate 100 mg, hydrochlorothiazide 12.5 mg
Selopress	AstraZenaca Pharma India Ltd., Bangalore.	10 Tablets	Metoprolol tartrate 100 mg, hydrochlorothiazide 12.5 mg
Drug Index, June-Aug., 2003[236]; Indian Drug Review, 2004[237].			

5.4.15. NEW DRUG APPROVAL BY US FDA MARCH 2002[238]

AstraZeneca LP got approval for its 25 mg TOPROL- XL extended release Metoprolol Succinate table form on 05 – March – 2002 through application No. 019962 in Original New Drug Application (NDA) with Rx status.

5.5. HYDROXYPROPYL METHYLCELLULOSE – CONTROL RELEASE POLYMER

5.5.1. Introduction

The word comes from the greek *polumeres,* which means 'having many parts[239]. Polymers are large molecules consisting of repeated chemical units ('mers') joined together usually in a line, like beads on a string[239]. The Dictionary of Science Technology, 1995[240] defines "polymer" as a large molecule formed by the union of atleast five identical monomers; it may be natural, such as cellulose or DNA, or synthetic, such as nylon or polyethylene; polymers usually contain many more than five monomers, and some may contain hundred and thousands of monomers in each chain.

5.5.2. Definition

Progress in polymer science made it increasingly apparent that some changes were needed in the basic terms used in polymer science. A need for clear and unambiguous definition of basic terms relating to polymers lead to second new glossary of terms formulated by the 1996 IUPAC Commission[241] containing 187 terms pertaining to polymer science.

Polymer Molecule (definition) [241]: A molecule of high relative molecular mass, the structure of which essentially comprises the multiple repetition of units derived, actually or conceptually, from molecules of low relative molecular masses.

Monomer (definition)[242]: A substance consisting of molecules, whic h can undergo polymerization, thereby contributing constitutional units to the essential structure of a macromolcule.

5.5.3. Hydroxypropyl methylcellulose (HPMC)

5.5.3.i. Synonyms[164,243]

Cellulose 2-hydroxypropyl methyl ether; hypromellose, Gonak; Goniosol; Tearsol; Methocel HG; Ultra Tears; lacril; Cellulose; hydroxypropyl methyl ether; Cluminal MHPC; Methocel; Metolose; Pharmacoat.

5.5.3.ii. Method of Preparation[244-245]

The polymer is prepared by reacting alkali-treated cellulose first with methylcellulose to introduce methoxy groups and then with propylene oxide to introduce propylene glycol groups at elevated temperature and pressure and for a reaction time sufficient to produce the desired degree of attachment of methyl and hyrdoxypropyl groups linkages to the anhydrous rings of cellulose. The resulting products are commercially available in different viscosity grades. The reason for its wide spread acceptance include –

(i) Solubility characteristic of polymer in gastro intestinal tract and in organic and aqueous solvent systems.

(ii) Non-interference with tablet disintegration and drug availability.

(iii) Flexibility, resistance and absence of taste and odor.

(iv) Stability in presence of heat, light, air or reasonable levels of moisture.

(v) Ability to incorporate color and other additives into the film without difficulty.

The interactions with this polymer is rare. HPMC closely approaches the desired attributes of an ideal polymer for film coating. When used alone, the polymer has the tendency to bridge or fill the debossed tablet surfaces. A mixture of HPMC with other

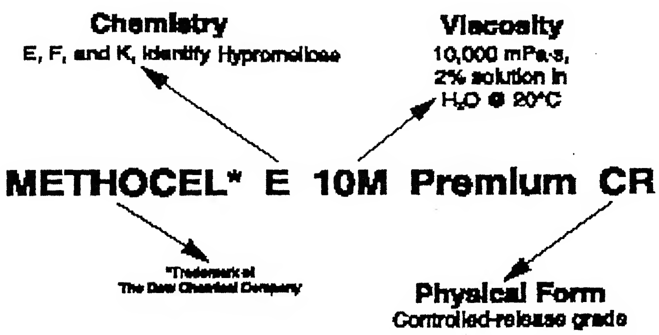
polymer or plasticizer is used to eliminate bridging or filling problems. This polymer is also used considerably in glossy solutions.

The approximate grade of methylcellulose is treated with NaOH and reacted with propylene oxide at elevated temperature and pressure and for a reaction time sufficient to produce the desired degree of attachment of methyl and hyrdoxypropyl groups linkages to the anhydrous rings of cellulose. The resulting products are commercially available in different viscosity grades. The details are given earlier in this chapter.

5.5.4. Commercial Products[246]

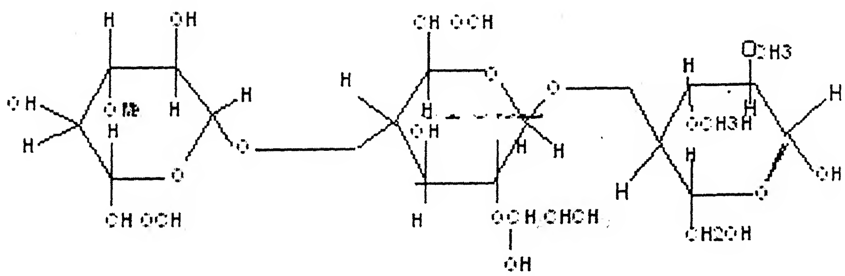
METHOCEL is a trademark of The Dow Chemical Company for a line of cellulose ether products. An initial letter identifies the type of cellulose ether, its "chemistry." "A" identifies methylcellulose (MC) products. "E," "F," and "K" identify different hypromellose products (Fig. 1). METHOCEL E and METHOCEL K are the most widely used for controlled-release drug formulations. The number that follows the chemistry designation identifies the viscosity of that product in millipascal-seconds (mPa·s), measured at 2% concentration in water at 20°C. In designating viscosity, the letter "C" is frequently used to represent a multiplier of 100, and the letter "M" is used to represent a multiplier of 1000. Several different suffixes are also used to identify special products. "P" is sometimes used to identify METHOCEL Premium products, "LV" refers to special low-viscosity products, "CR" denotes a controlled-release grade, and "LH" refers to a product with low hydroxypropyl content. "EP" denotes a product that meets European Pharmacopoeia requirements; "JP" grade products meet Japanese Pharmacopoeia requirements.

Figure 1: Example of nomenclature for a METHOCEL E cellulose ether



5.5.5. Properties

- Structure



- Appearance

  White or off-white, yellowish-white, grayish-white, practically odourless, hygroscopic fibrous powder or granules[247-248].

- Carbonization temperature: 280-300 ^{o}C[248].

- Surface Tension

  42-56 dyn/cm (2% aqueous solution)[248].

- Practically insoluble in hot water, dehydrated alcohol, acetone, chloroform, and ether; forms a colloidal solution in cold water; soluble in glacial acetic acid and in a mixture of equal volumes of alcohol and chloroform. A 1% solution in water has a pH of 5.5 to 8.0 granules[247]. The solubility varies with viscosity, the lower the

viscosity is, the higher solubility has. The different HPMC is different in some properties and its solubility in water is not affected by pH granules[248].

- The lower methoxy content in HPMC, the higher gelation temperature, the lower solubility in water and surface activity granules[248].
- HPMC has also other characteristics such as thickening property, pH stability, water retention, excellent film-forming property and good disperse and adhesion power granules[247-248].
- **Ionic Charge**[246-249]:

  No ionic charge (i.e., not a polyelectrolyte), do not complex with metallic salts and ionic organics to form insoluble precipitates. So they minimize interaction problems when used in acidic, basic, or other electrolytic systems, thus presenting less compatibility problems. Work well with soluble and insoluble drugs and at high and low dosage levels
- **Gel Formation**[249]

  Undergoes a reversible transformation from sol to gel upon heating and cooling, respectively.
- **Gel Point**[249]

(i) 50 – 90^{o}C, depending upon the Grade.

(ii) HPMC dissolves in both organic solvents and water over the entire biological pH range.

(iii) Aqueous solutions of HPMC gel on heating. Drastic increase in viscosity is observed near 60^{o}C. Therefore problems might be encountered at temperatures higher than this.

(iv) In gastric - fluid – soluble film coating, the water solubility of the film over the entire biological pH range directly influences the bioavailability of the active ingredients.

Table 5.16. Dissolution times of film from 6 cps HPMC in various solvents.

Test Fluid	Dissolution Time		
	20 °C	37 °C	50 °C
pH 1.2 (0.066 N HCl, 0.034 N NaCl)	2 min 01 sec	2 min 07 sec	6 min 10 sec
Water	1 min 51 sec	1 min 48 sec	3 min 17 sec
pH 7.5 (0.1 M phosphate buffer)	2 min 20 sec	3 min 48 sec	> 60 min
pH 10 (Kolthoff buffer)	2 min 00 sec	2 min 34 sec	40 – 45 min

Table 5.16 shows the dissolution times of film from 6 – cp – type HPMC (thickness 80 μm) in various fluids at 20, 37 and 50°C. There was no marked difference at 20°C. At 37°C, slight elongation of the dissolution time was observed in 0.1 M phosphate buffer (pH 7.5) and Kolthoff (pH 10), and the elongation was increased at 50°C. These changes are perhaps due to salting-out effect of increasing buffer concentration. At 50°C, the temperature is close to the thermal gelling temperature of HPMC so that the film becomes less soluble, and even if it disintegrates it remains in small fragments. From these data, it is expected that the film can be dissolved readily in the gastro intestinal tract at 37°C.

5.5.6. Molecular Weight and Viscosity[246]

Hypromellose, being a semi-synthetic material derived from cellulose, is a linear polymer comprised of therified anhydroglucose rings. The degree of polymerization (DP) is varied in production to give a polymer with the desired properties. For products typically used in controlled release applications, DP is adjusted to a range between 100 and 1500. Like all polymers, hypromellose macromolecules exist as a distribution and may be characterized by parameters such as the number average

molecular weight $\left(\overline{M_n}\right)$, the weight average molecular weight $\left(\overline{M_w}\right)$, and the polydispersity $\overline{M_n}/\overline{M_w}$.

5.5.7. Incompatibilities Granules[247]

It has been reported with a number of compounds including chlorocresol, hydroxybenzoates, and phenol. Large amounts of electrolytes increase the viscosity of methylcellulose mucilages owing to salting-out of methylcellulose, in very high concentrations of electrolytes; the methylcellulose may be completely precipitated.

5.5.8. Adverse Effects Granules[247]

Large quantities of methylcellulose may temporarily increase flatulence and distension and there is a risk of intestinal obstruction or condition likely to lead to intestinal obstruction. Oesophgeal obstruction may occur if compounds like methylcellulose are swallowed dry.

5.5.9. Precautions Granules[247]

Methylcellulose and other bulk laxatives should not be given to patients with intestinal obstruction or condition likely to lead to intestinal obstruction. They should be taken with sufficient fluid to prevent faecal impaction or oesophageal obstruction. Bulk laxatives lower the transit time through the gut and could affect the absorption of other drugs.

5.5.10. Safety[250]

Human and animal feeding studies have shown HPMC to be safe.

5.5.11. Use and Administration Granules

The physicochemical properties of HPMC[251] are strongly dependent on its chemical structure, and influences the following parameters: (i) methoxy content, (ii) hydroxypropyl content and (iii) molecular weight.

The swelling and solubility behavior of HPMC depends on the molecular weight, degree of substitution, cross-linking and grafting. Non-crosslinked polymer absorbs water, swell, and dissolve (erode); cross-linked HPMC swells to some equilibrium state, at which the retractive force of the network balances the swelling force.

The formation of a gel layer is of evident importance by the drug release from HPMC systems. Initially, the polymer is in a glassy state. Upon exposure to the respective biological fluid, water penetrated into the device and decreased the *Tg* of HPMC (acting as a plasticizer). With increasing water concentration, this reduction of the *Tg* also increases. At a critical concentration of water, the *Tg* equals the temperature of the system, and the polymer undergoes the transition from the glassy to the rubbery state. The increasing mobility of the macromolecular chains results in drug diffusion coefficients orders of magnitude higher than those in the glass state.

The reason for its wide spread acceptance include –

- Solubility characteristic of polymer in gastro intestinal tract and in organic and aqueous solvent systems.
- Non-interference with tablet disintegration and drug availability.
- Flexibility, resistance and absence of taste and odor.
- Stability in presence of heat, light, air or reasonable levels of moisture.
- Ability to incorporate color and other additives into the film without difficulty.
- The interactions with this polymer are rare.

The various grades of hydroxypropyl methylcellulose are widely for its various applications.

- **Emulsifying, suspending and thickening agent**

  Low viscosity grades are used to reduce the surface tension produced in the preparation of emulsions and in liquid oral dosage forms as replacements for sugar-based syrups or other suspension bases.

- **Thickening agent**

  High viscosity grades are used for thickening topically applied products such as gels and creams.

- **Granulating agent**

  In the manufacture of tablets low or medium viscosity grades are used as binding agents. High viscosity grades act as tablet disintegrants by swelling on contact with the disintegration medium.

- **Tablet coating**

HPMC closely approaches the desired attributes of an ideal polymer for film coating. When used alone, the polymer has the tendency to bridge or fill the debossed tablet surfaces. A mixture of HPMC with other polymer or plasticizer is used to eliminate bridging or filling problems. This polymer is also used considerably in glossy solutions. For tablet coating, high-substituted low viscosity grades are usually used.

- **Artificial Tears**

A 0.5 to 1% solution of high viscosity grade has been used as a vehicle for eye drops and as artificial tears and contact lens solution but hypromellose is now generally preferred for this purpose.

- **Wetting solution for contact lenses**

A wetting solution for contact lenses. Its demulcent action decreases the irritant effect of the lens on the cornea. It also imparts viscous properties to the wetting solution, which assists the lens in staying in place.

- **Laxative**

Medium and high viscosity grades are used as bulk laxatives since by taking up moisture they increase the volume of the faeces and promote peristalsis. They are usually given in the form of granules or tablets, in a dosage of 1 to 6 gm daily in divided doses taken with plenty of fluid. They are also given in similar doses with a minimum amount of water for the control of diarrhoea and in the management of osmotics and also used in the management of diventricular disease. Methylcellulose has also been used as an aid to appetite control in the management of obesity but there is little evidence of efficacy.

- **Controlled Drug Delivery**

Details are given in earlier section.

- **Food industry**

Methylcellulose is also employed as an emulsifier and stabilizer in the food industry.

- **Miscellaneous**

In adhesives, asphalt emulsions, caulking compounds, tile mortars, plastic mixes, cements, paints. As sticker for agriculture sprays and dusts.

5.6. LACTOSE MONOHYDRATE – EXCIPIENT[249,251, 253-254]

Synonym: Milk sugar, saccharum lactis, α-D-Lactose Monohydrate)

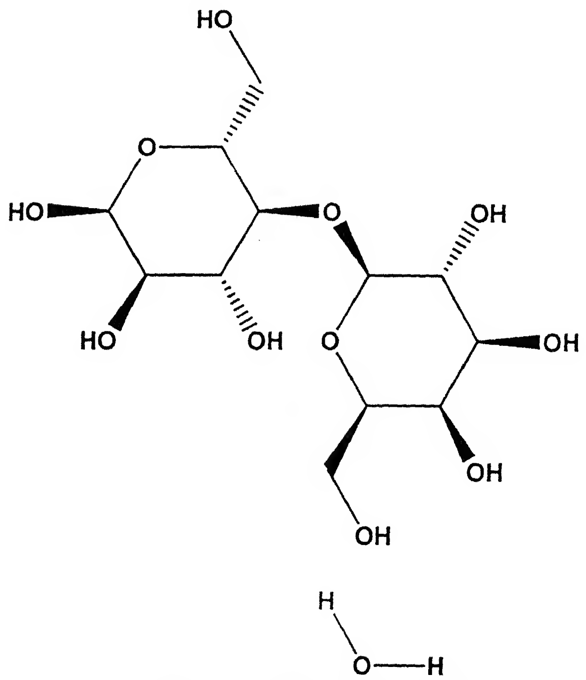
5.6.1. Description

White to off white or creamy-white crystalline particles or powder.

5.6.2. General Properties

- Empirical formula: a) $C_{12}H_{22}O_{11}$ (anhydrous), b) $C_{12}H_{22}O_{11}H_2O$ (monohydrate)
- Molecular weight: a) 342.30, b) 360.31

- Structure



- **LACTOSE MONOHYDRATE**

5.6.3. Typical Properties

- **Density**

Particle 1.52 g/cm^3 (α lactose monohydrate)

Bulk 1/77g/cm^3 (anhydrous)

Tapped 1.36g/cm^3 (anhydrous)

5.6.4. Solubility

Soluble in ammonia and acetic acid. Slightly soluble in dilute alcohols. Insoluble in chloroform, ether and absolute alcohol. In water, the details are given below.

Water	Cold	Boiling
α lactose monohydrate	20 g in 100 ml	38.4 g in 100 ml
β Lactose	45 g in 100 ml	91 g in 100 ml

- The β-D-Lactose content is less than 3%.

5.6.5. Types

Lactose occurs in 3 forms: α monohydrate, α anhydrous, β anhydrous. Odorless; sweet tasting. β-lactose is more soluble and slightly sweeter than α form.

- **α-lactose monohydrate**

Is the usual milk sugar and the lactose of pharmacy. One gram dissolves in 5 mL water, in 2.6 mL boiling water; very slightly soluble in alcohol. Insoluble in chloroform, ether. K_a at 16.5 $^{O}C = 6.03 \times 10^{-13}$.

- **β-lactose monohydrate**

One gram dissolves in 2.2 mL water at 15 ^{O}C, in 1.1 mL boiling water. After few days crystals of less soluble α-monohydrate appear from standing solutions.

5.6.6. Official Specifications

The details are given in Table 5.17.

Table 5.17. Pharmacopoeial Specifications for Lactose Monohydrate

Test parameter	Compendial Limits[253]
Description	Natural disaccharide, obtained from milk, which consists of one glucose and one galactose moiety.
Identification	A. Infrared Absorption. B. Chromatographic (TLC). Not more than 4 discernable spots as that of Reference Standard. C. A solution to which when ammonium hydroxide is added gives red color.
Clarity and color of colution	10% solution is clear and nearly colorless. Optical density at 400 m is not more than 0.04.
Melting point	121 –124 ^{O}C
Specific rotation	Between +54.4 ^{O} and +55.9 ^{O} determined at 20^{O} in 1.0% solution containing ammonium hydroxide.
pH	Between 6.0 and 7.0, in a 2.0% w/v solution.
Microbial Limits	The total aerobic microbial count does not exceed 100/gm, the total combined molds and yeasts count does not exceed 50/gm, and it meets the requirements of the test for absence of *Esherichia coli.*
Acidity or alkalinity	Dissolve 6 gm by heating in 25 mL of carbon dioxide – free

	water, cool, and add 0.3 mL of phenolphathalein TS; the solution is colorless, and not more than 0.4 mL of 0.1 N sodium hydroxide is required to produce red color.
Loss on drying	Dry it at 80 ^{O}C for 2 hours. The monohydrate from loses not more than 0.5% of its weight, and the modified monohydrate form loses not more than 1.0% of its weight.
Water	Between 4.5% to 5.5%, determined on a preparation containing lactose monohydrate in a mixture of methanol and formamide (2:1).
Residue on ignition	Not more than 0.1%, determined on a specimen ignited at a temperature of 600 ± 25 ^{O}C.
Heavy metals	Not more than 5 µgm/gm.
Protein and light absorbing impurities	1% (W/V) when measured in the range of 210 to 300nm, the absorbance divided by the pathlength in centimeters is not more than 0.25 in the range of 210 to 220 and is not more than 0.07 in the range of 270 to 300 nm.

5.6.7. Applications

- Solid dosage form: Diluent, bulking agent, filler and excipient for compressed and molded tablets and capsules.
- An ingredient in infant foods.
- Lyophilized products: Added to freeze dried solutions to increase plug size and aid caking.
- Sugar coating: Lactose is used in combination with sucrose for sugar coating solutions.

5.6.8. Use

Both α and β forms of lactose are employed, with the α-form predominating; as a nutrient in preparing modified milk and food for infants and convalescents.

- In baking mixtures.
- Pharmaceutical Aid – (tablet and capsule excipient and diluent).
- To produce lactic acid fermentation in ensilage and food products.
- As chromatographic adsorbents in analytical chemistry.
- In culture media.

- Therapeutic category (Veterinary)
- Added to cow's milk for feeding orphan foals.

5.6.9. Incompatibilities

The 'browning reaction' is base catalyzed and may therefore be accelerated if alkaline lubricants are used.

5.6.10. Safety[252]

Intolerance to lactose in persons with a deficiency of intestinal *lactase* and may lead to abdominal cramps, diarrhea, distension and flatulence. In lactose tolerant individuals, the enzyme *lactase* hydrolyzes lactose in the small intestine to glucose and galactose, which are absorbed. It is not uncommon for humans to lose the ability to hydrolyze lactose as they mature. The incidence of adult *lactase* deficiency (hypolactasia) varies considerably among different populations.

5.7. MAGNESIUM STEARATE – EXICPIENT[255,256]

- Synonym: Metallic stearate, Magnesium salt.

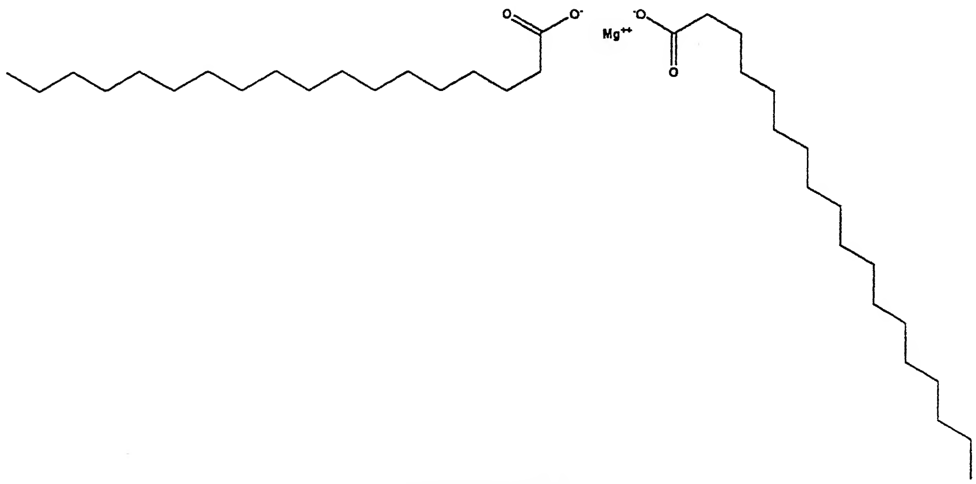
5.7.1. Description

Octadeconoic acid magnesium salt. Fine, white, precipitated or milled, impalpable powder of low bulk density. Odor and taste are slight but characteristic. The powder readily adheres to the skin. The commercial preparation also contains palmitate.

5.7.2. General Properties

- Empirical Formula: $C_{36}H_{70}MgO_4$
- Molecular Weight: 591.3

- Structure



MAGNESIUM STEARATE

5.7.3. Typical Properties

- **Solubility**

  Insoluble in water, alcohol and ether. Slightly soluble in hot alcohol and benzene.

- **Stability and storage conditions**

  Stable, non-self-polymerizable. Store in a cool, dry place in a well closed container.

- **Incompatibilities**

  Acidic substances; alkaline substances; iron salts. Avoid mixing with strong oxidizing materials. Use with caution with drugs, which are incompatible with alkali.

5.7.4. Mechanism of Action

In order to reduce die wall friction and therefore obtain greater uniformity in the compact, lubricant magnesium stearate at 5% of tablet weight is added in the tablet formulation[257]. Tablet lubricants act by interposing a film of low shear strength at the interface between the die-wall and the compact, thus reducing the friction.

Tablet lubricant may act in one or all of the three ways: (i) as anti-adhesive to prevent the tablet-form sticking to the die wall and the punch faces; (ii) to reduce sliding friction at the die wall; and (iii) as glidants that will promote free flowing properties of the powder or granules into the die.

It is evident that tablet lubricants act by interposing a film of lower shear strength at the interface between the die-wall and the compact, thus reducing the friction force. Die-wall lubricants must have low shear strength. From mechanical considerations, as low a value of shear strength as possible is desirable. This suggests that liquid lubricants (hydrodynamic lubricants) might be more suitable than the solid lubricants (boundary lubricants) normally used.

Tablet lubricants are most effective when used in a fine degree of subdivision. Since their function is related to surfaces, the greater the degree of subdivision, the greater the area they can cover. Therefore, they are usually passed through 60-mesh or finer screens before their incorporation into the granulation. Lubricants usually are added at the very last step before compression, since they must be present on the surfaces of the granules and in-between them and the parts of the tablet press.

Table 5.18. Shear strength values of various lubricants.

Lubricants	**Shear strength (kg/cm^2)**
Magensium stearate	20.0
Potassium stearate	31.3
Sodium stearate	33.9
Talc with grain	63.2
Talc across grain	80.0
Zinc stearate	9.3 – 20.2

5.7.5. Pharmacopoeial Specification

The details are given in Table 5.19.

Table 5.19. Pharmacopoeial Specifications for Magnesium Stearae

Test parameter	Compendial Limits[258-259]
Description	Magnesium stearate is a compound of magnesium with a mixture of solid organic acids, and consists chiefly of variable proportions of magnesium stearate and magnesium palmitate. The fatty acids are derived from edible sources. It contains not less than 4.0% and not more than 5.0% of Mg, calculated on the dried bases.
Identification	A. Chemcial Test: The ether extract complies with identification test for magnesium. B. Chromatographic (HPLC). The retension times of the peaks corresponding to steric acid and palmitic acid in the chromatogram of the System suitability solution; as obtained in the Relative content of stearic acid and palmitic acid test.
Microbial Limits	The total aerobic microbial count does not exceed 1000/gm, the total combined molds and yeasts count does not exceed 500/gm, and it meets the requirements of the test for absence of *Salmonella* species and *Esherichia coli.*
Acidity or alkalinity	Tansfer 1.0 gm to a 100-ml beaker, add 20 mL of CO_2-free water, boil on a stem bath for 1 minute with continuous shaking, cool, filter. Add 0.05 mL of bromothymol bule TS fo 10 mL of the filterate: Not more than 0.05 mL of 0.1 N hydrochloric acid or 0.1 N NaOH is required to change the color of the indicator.
Loss on drying	Not more than 6.0% of its weight at 105 ^{O}C.
Specific Surface Area	The P/P_0 range lies between 0.05 to 0.15 using outgassing conditions of 2 hours at 40 ^{O}C.
Limit of chloride	The test solution shows no more chloride than corresponds ot 1.4 mL of 0.020 N hydrochloric acid (0.1%).

5.7.6. Functional Category

- USP: Tablet and/or capsule lubricant
- BP/EP: Lubricant; Pharmaceutical aid
- Other: Glidant, Anti-adherent
- It is generally used at 0.25 – 2.0%.
- It is also used in baby dusting powders.

5.7.7. Safety

It is described as an inert or nuisance dust. Classified as non-hazardous by the department of Transportation Regulations. Dust clouds of magnesium stearate may be explosive.

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Chapter 6

Introduction To Experimental......

6.1. DOSE CONSIDERATION[1-6]

Duration of most illness is longer than therapeutic effect produced by a single dose. An optimal multiple dosage regimen is the one in which the drug is administered in suitable does, with sufficient frequency that ensured maintenance of plasma concentration within the therapeutic window.

The degree of fluctuation between the highest and lowest plasma concentrations C_{max} and C_{min} is proportional to dose size. Similarly if the dosing frequency is reduced, the plasma concentrations produced are lower and the ratio C_{max}/C_{min} are higher. Higher dose and frequency, results in greater accumulation and toxicity. Generally, dosing frequency similar to plasma half-life of the drug ($T=t_{½}$) leads to better therapeutic success.

Generally five half lives or doses are required to achieve reasonably constant plasma concentrations. To avoid this delay, priming or loading does is administered followed by regular doses or maintenance doses. The loading dose, which may be up to about twice the maintenance dose, pushes the plasma concentration to desired level, which is then maintained by the maintenance doses.

In case of controlled/extended release orally dosage forms, assuming that (i) drug disposition follows first-order kinetics, (ii) the rate-limiting step in the absorption is rate of drug release from the formulation, and (iii) the released drug is rapidly and completely absorbed, four general models for drug input based on the drug release pattern can be defined: (i) zero-order release, (ii) first-order release, (iii) initial rapid first order release of loading dose followed by zero-order release, and (vi) initial rapid first order release of loading dose followed by first-order release.

If the drug released from ER formulations is stable zero-order in fluids at the absorption site and has similar absorption efficiency from all encountered absorption sites, its rate of appearance in plasma will be governed by its rate of release. Thus, in this case chances of obtaining flatter plasma concentration will be better. First order release systems, although easier to design, have limitation compared to zero-order systems. This is because with first order release characteristic, release rate falls with time as the formulation advances along intestinal tract; the absorption efficiency generally decreases due to reason likes (i) reducing surface area, (ii) increasing viscosity, and (iii) decreasing mixing. In case of last two models i.e., "initial rapid first order release", an initial dose is rapidly release (immediate release fraction) for immediate first-order availability, while the remaining amount is released (sustained release fraction) at a slow zero or first order. Both the fractions are built in the same unit of the dosage form e.g., tablets. Such a formulation is ideally suited for drugs with long $t_{½}$ in which case attainment of plateau would have otherwise taken a long time. The slow release component should ideally begin releasing the drug when the drug level from the faster release component is at the peak. Repeated administration of such type of dosages may result into increased fluctuations in the plasma concentration. To minimize this, one could plan for

(i) Decreasing the loading dose in the subsequent dosage forms,

(ii) Increasing the dosing interval, or

(iii) Incorporating sufficiently small portion of the drug in the immediate release fraction.

Usually the last mentioned option is most suitable.

Various pharmacokinetic models[7-12] are proposed for calculating dose and release profile of ER dosage form. According to model proposed by *Rowland* and *Beckett*, Total dose (*W*) in ER formulation is given by

$$W = (W_0 + 0.693\, W_0 .\, f.\, h)\,/t_{½} \qquad (6.1.)$$

where	W_0	=	dose giving clinical response in conventional dose
	f	=	absorption factor
	$t_{½}$	=	half life
	h	=	number of hours.

According to model proposed by *Dobrinska* and *Welling*,

Total dose (W) in ER formulation is given by

$$W = (C_{ss} \,.\, V_d \,.\, K_{el} \,.\, T.) + (C_{ss} \,.\, V_d \,.\, K_{el}) \,/\, K_{el} \qquad (6.2)$$

where	C_{ss}	=	steady state plasma concentration
	V_d	=	volume of distribution
	K_{el}	=	elimination constant
	T	=	number of hours.

In this work zero order and first order release models based on the above models is attempted.

6.2. ORAL EXTENDED RELEASE SYSTEM

Over the past two decades, ER Dosage Form particularly, multi-particulate oral drug delivery (DD) and oral matrix DD have become extremely popular for controlling the release of drug from solid dosage form. They are the focus of pharmaceutical dosage form technology and are been continuously developed in order to enhance clinical efficiency and reduce total disease management cost, thereby providing economic merit to the society. The term “ER dosage form” can be used for dosage forms to indicate that the drug release kinetics is predictable and reproducible from one unit to another, whether or not the kinetics followed is zero order.

6.2.1. Continuous Extended Release System

These systems release the drug for a prolonged period of time along the entire length of *g.i.t.* especially up to the terminal region of small intestine, with normal transit of the dosage form. These systems are:

(i) Dissolution controlled release systems

(ii) Diffusion controlled release systems

(iii) Dissolution and diffusion controlled release systems

(iv) Ion-exchange resin-drug complexes

(v) Slow dissolving salts and complexes

(vi) pH-dependent formulations

(vii) Osmotic pressure controlled systems

(viii) Hydrodynamic pressure controlled systems

6.2.2. Delayed Transit And Continuous Release System

These systems are designed to prolong their residence in the *g.i.t.* along with their release. Often, the dosage form is fabricated to retain in the stomach and hence the drug present therein should be stable to gastric pH. Systems are:

- Altered density systems
- Size-based systems
- Mucoadhesive systems

6.2.3. Delayed Release System

These systems include drugs, which are unstable under certain conditions of *g.i.t.*, may cause *g.i.t.* distress, absorbed from a specific *g.i.t.* site or meant to exert local effects at a specific *g.i.* site. Systems are

- Intestinal release systems
- Colonic release systems

In this work, the first variety i.e., continuous release systems incorporating diffusional mechanisms and /or dissolution is attempted.

6.3. PREFORMULATION STUDIES

"It is a capital mistake to theorize before one has data",

Scandal in Bohemia, Sir Arthur Conan Doyle.[13]

Preformulation can be defined as a reconnaissance in depth to define the properties of a drug molecule likely to affect the design and performance of the drug delivery system (DDS). Although preformulation data do not necessarily tell us which path to follow in formulation work, it very often does inform us which path are dead ends. Originally, preformulation was largely concerned with how possible incompatibilities between drugs and excipients might affect the stability of drug formulation. However, when, during the 1960's an increasing body of experimental data clearly demonstrated the deficiencies *in vivo* of then commercialized drug products, the biopharmaceutical aspects of preformulation became increasingly important[14].

Preformulation is the study of the chemical and physical properties of the drug compounds prior to the developmental process of the formulation. The purpose of the study is to understand the nature and characteristic of each component and to optimize conditions of the dosage form manufacture. Before development, preformulation data must be generated to aid development process and physicochemical properties must be defined. The interaction (excipient compatibility) between the drug and the excipients to be used in the formulation are included in the study for intelligent selection of excipients. Drug degradation profiles are also to be included in the study. Analytical characteristics are included for development of technique, so as to monitor process during formulation development stage. Stages of preformulation include[15]:

- Preformulation report on physicochemical properties and analytical testing of drug.
- Preformulation report on data for development of dosage form.
- Preformulation report on data to support for Quality and Finished product Manufacturing.

6.3.1. Preformulation Reports[15]

Preformulation studies report include

- **Analytical Profiles** as is required for analytical method development, which include identification technique of drug, purity studies that include degradation and residual solvent analysis, and chemical properties of drug.

- **Physiochemical Properties** such as partition coefficient, dissociation constant, pKa, solubility. pKa can be estimated using *Henderson-Hasselbalch* equation from UV spectrophotometry, titration or solubility studies. Solubility studies are essential from understanding bioavailability (absorption of drug) and setting up *in vitro* dissolution techniques. Solubility studies are carried in solution (pH 1.0 to 7.5) and in solvents.

- **Pharmaceutical and Mechanical Properties**, which will include hygroscopicity and moisture absorption/desorption, powder characteristics – density, flow and compression property.

- **Solid-state Characteristics** such as solid state, particle size, surface aera, biopharmaceutical properties, polymorphism, hydrates and solvates.

- **Excipient Compatibility** for selection of excipient. This study focuses on binary mixture of drug substances and selected excipient in fixed ratio with or without water. The mixture is stored at elevated temperature in capped vials. The results of interaction may be determined by visual observation, TLC, HPLC, UV and DSC.

However, the importance attached to stability aspects of preformulation has in many companies tended to decrease[14]. *Monkhouse*[16-17] has argued articulately and powerfully that some types of preformulation tests for incompatibilities are academic in the worst sense of word. He has indicated that studies in which powder mixtures of say 50% drug and 50% excipient exposed to storage at elevated temperature may well show interactions, but whether or not such interactions are of practical importance may well be debatable. In the finished dosage form, the excipient may only be present at the 1% level and drug at 1%. Under such conditions, the formulation, may well prevent the incompatibility from ever having any practical effect. As a result of these criticisms and, in some cases, after examination of their own experimental data, certain companies in the pharmaceutical industry have recently reduced the scope of their incompatibility testing. However, stability studies of the pure drug substance remain an essential part of preformulation studies. Besides, this, it forms a regulatory requirements for NDA's by FDA and other regulatory agencies.

The different techniques employed for the evaluation during the preformulation studies are:

6.4. SPECTRAL METHODS USED FOR CHARACTERIZATION DURING PREFORMULATION

The most often-employed spectral study methods include (a) absorption spectroscopy; (b) infra red spectroscopy; and (c) X-ray diffraction spectroscopy.

All atoms and molecules are capable of absorbing energy in accordance with certain restrictions; these limitations depend upon the structure of the substance. The kind and amount if radiation absorbed by a molecule depend on the structure of molecule,

the amount of radiation absorbed also depends upon the number of molecules interacting with the radiation.

6.4.1. Absorption Spectroscopy

Absorption spectroscopy is one of the most valuable analytical techniques invented. Its advantages include speed, simplicity, specificity and sensitivity.

Methods	Wavelength range (in nm)
Ultra-violet	185-380
Visible	380-780
Near Infra-red	780-3000
Far Infra-red	3000-40,000

6.4.2. Ultra-Violet Visible Spectroscopy[18-20]

Principle: When radiation is passed through a layer of a solution containing an absorbing substance, part of the radiation is absorbed; the intensity of the radiation emerging from the solution is less than the intensity of the radiation entering it. The magnitude of the absorption is expressed in terms of the absorbance, *A*, defined by the expression

$$A = \log_{10} (I_0/I) \tag{6.3}$$

where I_0 = intensity of the radiation passing into the absorbing layer

I = intensity of the radiation passing out of it.

The absorbance depends on the concentration of the absorbing species in the solution and the thickness of the absorbing layer for measurement.

The absorption spectra of a compound can be measured in very dilute solution against a solvent blank using an automatic recording spectrophotometer. For

colorless compounds, measurements are made in the range of 200-400 nm, for colored compounds, the range is 400-700 nm.

UV-visible spectroscopy can be used to determine many physicochemical characteristics of compounds and thus can provide information as to the identity of a particular compound.

Although UV-visible spectra do not enable absolute identification of an unknown, they are frequently used to confirm the identity of a substance through comparison of the measured spectrum with a reference spectrum. Where spectra are highly similar, derivative spectroscopy may be used. Derivative spectra can be useful in qualitative analysis, either for characterizing materials or for identification purposes. Derivative spectra can be used to enhance difference among spectra, to resolve overlapping bands in qualitative analysis and, most importantly, to reduce the effects of interferences from scattering, matrix, or other absorbing compounds in quantitative analysis.

6.4.3. Calibration of UV-Visible Spectrophotometer

Various parameters to be calibrated for UV-Visible spectrophotometer include (i) accuracy; (ii) wavelength accuracy; (iii) stray light (220 nm and 340 nm); (iv) drift; and (v) noise. Most commonly recommended method for checking absorbance accuracy is to use solution of potassium dichromate (6.006 mg/100mL in 0.005 N H_2SO_4). It exhibits characteristic spectral graph having minima (valley) at 235 nm, 313 nm; and maxima at 257 nm and 350 nm.

Filters having calibration traceable to international standards can also be used for checking the various parameters. Usually, a set of four neutral density filters is

available. Holmium filter for absorbance accuracy, Didymium filter for wavelength accuracy and two filters designed to assess stray light at 220 nm and 340 nm. Also 1.2% solution of KCl can be used to check the level of stray light. For calibration of wavelength, tolerance of ± 1 nm in the range of 200-400 nm and ± 3 nm in visible range is usually recommended.

6.4.4. Infra Red Spectroscopy[18-20]

Infrared radiation refers broadly to that part of the electromagnetic spectrum between the visible and microwave region. It can be divided into the near infrared region (0.7 –2.5 μm) and the far infrared region (14.3 – 50 μm).

The frequencies of the normal vibrations of molecules, i.e., the position of the spectrum bands obtained (expressed in wavelengths or in wave numbers) are determined by the masses of the atoms of the molecules and the forces acting between the masses. Consequently infrared spectra are individual to a high degree.

Although the infrared spectrum is characteristic of the entire molecule, it turns out certain groups of atoms giving rise to bands at or near the same frequency regardless of the structure of the rest of the molecule. It is the persistence of these characteristic bands that permits obtaining useful structural information by simple inspection and reference to generalized charts of characteristic group frequencies.

The fact that many functional groups can be identified by their characteristic vibration frequencies makes the IR spectrum the simplest and often the most reliable method of assigning a compound to its class. IR spectroscopy is most frequently used as a fingerprinting device. The complexity of the IR spectrum lends itself particularly well

to this purpose and such comparisons are very important in the complete identification of many compounds.

IR spectra may be measured in an automatic IR spectrophotometer either in solution (in chloroform or carbon tetrachloride 1-5%), as a mull with nujol oil or in the solid state mixed with KBr.

6.4.5. Calibration

The IR spectrophotometer should be calibrated so that the bands are observed at their proper frequencies or wavelengths. Proper calibration can be made with reliable standards such as polystyrene film.

6.4.6. Advances

Earlier dispersive spectrophotometers, introduced in the mid – 1940s were widely used, since they provided the robust instrumentation required for the extensive application of this technique. Now days, fourier transform spectrophotometers have replaced dispersive instruments for most applications due to their superior speed and sensitivity. They have greatly extended the capabilities of infrared spectroscopy and have been applied to many areas that are very difficult to nearly impossible to analyze by dispersive instruments. Instead of viewing each component frequently sequentially, as in a dispersive IR spectrophotometer, all frequencies are examined simultaneously, in Fourier Transform Infra Red (FTIR) spectroscopy.

Photoacoustic spectroscopy (PAS) is a useful extension of IR spectroscopy and is suitable for examining highly absorbing samples that are difficult to analyze by conventional IR techniques.

6.5. NON-SPECTRAL METHODS USED FOR CHARACTERIZATION DURING PREFORMULATION (Physical Methods)

6.5.1. Determination of Density

The bulk density of the solid is often very difficult to measure since the slightest disturbance of the bed may result in a new bulk density. Moreover, it is clear that the bulking properties of a powder are dependent on the "history" of the powder (e.g., how it was handled), and that it can be packed to have a range of bulk densities. Thus, it is essential in reporting bulk density to specify how the determination was made. Because the inter-particulate interactions that influence the bulking properties of a powder are also the interactions that interfere with powder flow, a comparison of the bulk and tapped densities can give a measure of relative importance of these interactions in a given powder. Such a comparison is often used as an index of the ability of the powder flow. The bulk density often is the bulk density of the powder "as poured" or as passively filled into a measuring vessel. The tapped density is a limiting density attained after "tapping down", usually in a device that lifts and drops a volumetric cylinder containing the powder a fixed distance.[21]

6.5.2. Bulk Density[21]

Bulk density is determined by measuring the volume of a known mass of powder sample that has been passed through a screen into a graduated cylinder (Method I) or through a volume-measuring apparatus into a cup (Method II).

Method I: Measurement in a Graduated Cylinder

Procedure: Unless otherwise specified, pass a quantity of material sufficient to complete the test through a 1.00-mm (No.18) screen to break up agglomerates that may have formed during storage. Into a dry 250-mL cylinder introduce, without

compacting, approximately 100 gm of test sample, *M*, weighed with 0.1% accuracy. It is not possible to use 100 gm the amount of the test sample and the volume of the cylinder may be modified and the test conditions specified with the results. Select a sample mass having an untapped apparent volume of 150 to 250mL. A 100-mL cylinder is used for apparent volumes between 50mL and 100mL. Carefully level the powder without compacting, if necessary, and read the unsettled apparent volume, V_O, to the nearest graduated unit. Calculate the bulk density, in gm/mL, by the formula

$$\textbf{Bulk/ Fluff density} = (M)/(V_O)\,gm/mL \qquad (6.4)$$

Generally replicate determinations are desirable for the determination of this property.

6.5.3. Tapped Density[21]

Tapped density is achieved by mechanically tapping a measuring cylinder containing a powder sample. After observing the initial volume, the cylinder is mechanically tapped and volume readings are taken until little further volume is observed. The mechanical tappings are achieved by raising the cylinder and allowing it to drop under its own weight a specified distance by either of two methods as described below. Devices that rotated the cylinder during tapping may be preferred to minimize any possible separation of the mass during tapping.

Method I

Procedure: Unless otherwise specified, pass a quantity of material sufficient to complete the test through a 1.00 mm (No. 18) screen to break up agglomerate that may have formed during storage. Into a dry 250-mL glass graduated cylinder (readable to 2 mL) weighing 220 (±44) gm and mounted on a holder weighing 450 (±10) gm introduce, without compacting, approximately 100 gm of test sample, *M*,

weigh with 0.1% accuracy. If it is not possible to used 100 gm, the amount of the test sample may be reduced and the volume of the cylinder may be modified by using a suitable 100-mL graduated cylinder (readable to 1 mL) weighing 130 (±16) gm and mounted on a holder weighing 240 (±12) gm.

The modified test conditions are specified with the results. Carefully level the powder without compacting, if necessary, and read the unsettled apparent volume, V_O, to the nearest graduated unit.

Mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using a suitable mechanical tapped density tester that provides a fixed drop of 14 ±2 mm at a nominal rate of 300 drops per minute. Unless otherwise specified, tap the cylinder 500 times initially and measure the tapped volume V_a, to the nearest graduated unit. Repeat the tapping an additional 750 times and measure the tapped volume, V_b, to the nearest graduated unit. [NOTE: Fewer taps may be appropriate, if validated for some powder]. If the difference between the two volumes is less than 2%, V_b is the final tapped volume, V_f. Repeat in increments of 1250 taps, as needed, until the difference between succeeding measurements is less than 2%. Calculate the tapped density, in gm per mL, by the formula

$$\textit{Tapped density} = (M)/(V_f)\ gm/mL \qquad (6.5)$$

Generally replicate determinations are desirable for the determination of this property.

Method II

Proceed as directed under Method I except that a suitable mechanical tapped density tester that provides a fixed drop of 3 mm (±10%) at a nominal rate of 250 drops per minute is used.

6.5.4. Measurement Of Powder Compressibility[21]

The Compressibility Index and *Hausner* Ratio are measures of propensity of a powder to be compressed. As such, they are measures of the relative importance of inter-particulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter-particle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index and the *Hausner* Ratio.

6.5.4.i. Compressibility Index: Calculate by the formula

$$100(V_O - V_f)/V_O \tag{6.6}$$

6.5.4.ii. *Hausner* Ratio: Calculate by the formula

$$V_O/V_f \tag{6.7}$$

6.5.5. Flow Property[13, 22-23]

A bulky powder is somewhat analogous to a non-Newtonian liquid, which exhibits plastic flow and sometimes dilatancy, the particles being influenced by attractive forces to varying degrees. Accordingly powders may be free flowing or cohesive and "sticky". With small particles (less than 10µm); particle flow through orifice is restricted because the cohesive forces between the molecules are often of the same magnitude as gravitational forces. As the particle size increase the in flow is obtained, however, a maximum flow rate is reached after which flow decreases as size of the particles approach that of the orifice.

Powder flow property may be increased by (a) removing the fines and (b) adsorbing them onto larger particles. Occasionally poor flow may result from presence of moisture, in which case drying is beneficial.

Elongated or flat particles tend to pack, albeit loosely, to give powders with a high porosity. Particles with high density and low internal porosity tend to possess free flowing properties. Free flowing powders are characterized by "dustibility". This property can, however be offset by surface roughness, which leads to poor flow characteristics due to friction and cohesiveness.

A static heap of powder, when only gravity acts upon it, will tend to form a conical mound. One limitation exists: the angle of the horizontal cannot exceed a certain value, and this is known as the angle of repose (Φ). If any particle temporarily lies outside this limiting angle, it will slide down the adjacent surface under the influence of gravity until the friction caused by interparticulate forces balances the gravitational pull. Accordingly there is an implied relationship between Φ and flow and particle shape. The exact value for Φ depends on the method of measurement.

The tangent of the angle of repose is equal to the coefficient of friction "µ" between the particles.

$$\tan \Phi = \mu \qquad (6.8)$$

Hence, the rougher and more irregular the surface of the particle, the higher will be the angle of response. Values of Φ are rarely less than 20^{O} and values upto 40^{O} indicate reasonably flow rates. Above 50^{O}, however the powder flows only with great difficulty.

Apparatus: According to the flow properties of the material to be tested, funnels with or without stem with different angles and orifice diameters are used. The funnel is maintained upright by a suitable device. The assembly must be protected from vibrations.

The angle of repose can be calculated using the formula

$$\tan \Phi = h/r \qquad (6.9)$$

therefore $\Phi = \tan^{-1}(h/r)$ (6.10)

The area of the circle is calculated as

$$\textit{Area of a circle} = \pi r^2 \quad (6.11)$$

therefore $r = (\text{area of circle}/\pi)^{1/2}$ (6.12)

Angle of repose has a significant and critical role in tablet manufacture. It governs the properties as (i) fill quantity in the die, (ii) weigh variation, (iii) content uniformity, (v) hardness and (vi) friability etc.

6.5.6. Water Content[24-25]

The term moisture usually defined as wetness conferred by an unidentified liquid is assumed to be due to water. Moisture in pharmaceutical substance is significant. It affects (i) chemical stability, (ii) crystal structure and (iii) powder flow etc. Process such as wet granulation, mixing extrusion, spheronization, drug loading, tray drying, are some operations, which depend on the amount and state of water present. Moisture can and does influence the properties of individual's active ingredients and excipients and it is essentially, to characterize the effect o moisture on these individual components.

The USP offers two methods for the determination of Moisture Content in solids: (i) Tritrimetry (*Karl Fischer* Titration) and (ii) Gravimetry. Most articles listed in official compendia contain specifications on water or "Loss on Drying". Since volatile components other than water may be present, "LOD" is no effective moisture content determination technique. These gravimetric techniques recommend use of drying till constant weight under vacuum in oven or modern techniques of infrared or microwave based moisture microbalances.

In its simplest form, *Karl Fischer* titration is one point determination of moisture content. Its principle advantage are: (i) specificity for water, (ii) it is non-thermal method, (iii) highly sensitive, and (iv) the process can be automated. The main disadvantage is that the solid must dissolve in the titration medium. To be sure that the total amount of moisture is released; however, if analysis carefully designed in such a way that moisture is extracted from the solid to the same degree each time; accurate and reproducible results can be obtained for solids that do not dissolve.

6.5.7. Particle size and size distribution

Particle size distribution of drugs, polymer, excipients, granules etc. have profound effect on the mixing phenomenon. Absence of electrostatic charge can result into uniform blends. Particle size also has influence on the dissolution of the drug, which in turn influences the bioavailability. The most common method used to evaluate particle size distribution is optical microscopy, sieve analysis, laser light scattering and electrical zone sensing.

6.5.7.i. Microscopy: It is useful as a means to obtain estimations of the particle distribution in a sample. Determination can also be easily made regarding the relative crystallinity and crystallographic information of the material. Evaluation of the morphology of a pharmaceutical solid is also possible, which is of extreme importance, because this property exerts a significant influence on the overall micromeritic and bulk properties of the material. Both optical and electron microscopes are widely used to characterize pharmaceutical solids. Optical microscopy is limited to the range of magnification suitable for routine work, that is, an approximate upper limit of 600X. However, this magnification limit does not preclude the investigation of most pharmaceutical materials, and the use of polarizing optics induces a power into the technique that is not available – with other methods.

Electron microscopy gives excellent three dimensional, topographic and shape of the object.

6.5.7.ii. Sieving[26-27]: Sieving is one of the oldest methods of classifying powders by particle size distribution. Sieving is most suitable where the majority of the particles are larger than about 75 μm, although it can be used for some powders having smaller particle sizes where the method can be validated. In pharmaceutical terms, sieving is usually a method of choice for classification of the coarser grades of single powders. It is particularly attractive method in that powders are classified only on the basis of particle size, and in most cases the analysis can be carried out in the dry state.

Among the limitation of the of sieving method are: (i) The need for an appreciable amount of sample (normally at least 25 gms), and (ii) Difficulty in sieving oily or other cohesive powders that tend to clog the sieve openings.

The method is essentially a two-dimensional estimate of size because passage through the sieve aperture is frequently more dependent on maximum width and thickness than on length. This method is intended for estimation of the total particle size distribution of a single material. It is not intended for determination of the proportion of particles passing or retained on one or two sieves.

Significant parameters involved in analytical sieving.

(i) The method is generally intended for use where at least 80 % of the particles are larger than 75 μm.

(ii) The size parameter involved in determining particle size distribution by analytical sieving is the length of the side of the minimum square aperture through which the particle will pass.

Dry Sieving Method (Method I) : Tare each test sieve to the nearest 0.1 gm. Place an accurately weighed quantity of test specimen on the top (coarsest sieve, and replace the lid). Agitate to validated (over established end-point determination) fixed time of sieving.

Interpretation: The raw data must include the weight of test specimen, the total sieving time, and the precise sieving methodology, in addition to the weights on the individual sieves and in the pan. It may be convenient to convert the raw data into a cumulative weight distribution and if it is desired to express the distribution in terms of a cumulative weight undersize, the range of sieves used should include a sieve through which all the material passes. If there is evidence on any of the test sieves that the material remaining on it is composed of aggregates formed during the sieving process, the analysis is invalid.

Sieving procedure is relatively simple, involving mechanical sieve shaker to shake the nest of sieves arranged in descending order. Fraction retained on each sieve is calculated.

6.5. TABLET DOSAGE FORM

6.6.1. Desirable properties of Tablets

- The tablet must be sufficiently strong and resistant to shock and abrasion to withstand handling during manufacture, packaging, shipping and use. This property is measure of two tests: hardness and friability.
- Tablets must be uniform in weight and in drug content of the individual tablet. This is measured by the weight variation test and the content uniformity tests.
- The drug content of the tablet must be bioavailable. This property is also measured by two tests: disintegration test and dissolution test. However,

bioavailability of a drug from a tablet, or other dosage form, is a very complex problem and the results of these two tests do not of themselves provide an index of bioavailability. This must be done by monitoring levels of the drug in blood or other bio-fluids.

- Tablets must be elegant in appearance and must have the characteristic shape, color and other marking necessary to identify the product. Markings are usually the monogram or logo of the manufacturer. Tablets often have a code number printed or embossed on the surface of the tablet corresponding to the in-house documentation or as per FDA. Another marking that may appear is to permit breaking the tablet into equal parts for the administration of half tablet. However, it has been shown that substantial variation in drug dose can occur in the manually broken tablets.

6.6.2. Tablet Formulation Considerations

- Size of the dose and quantity of active ingredient.
- Stability of the active ingredient.
- Solubility of the active ingredient.
- Density of the active ingredient.
- Compressibility of the active ingredient.
- Selection of the excipients.
- Method of granulation.
- Character of granulation.
- Tablet press, type, size, and capacity.
- Environmental conditions (temperature, dust and humidity control).
- Stability of the final product.
- Bioavailability of the active drug content in the tablet.

The selection of excipients is critical in the formulation of tables. Once the formulator has become familiar with the physical and chemical properties of the drug, the

process of selecting excipients is begun. The stability of the drug should be determined with each proposed excipients.

6.6.3. Techniques for manufacture of extended release tablets

The techniques, equipment and steps involved in manufacturing of immediate release tablets can be used for manufacturing of extended release tablets. Therefore, they enjoy popularity amongst the manufacturer since their manufacturing may not require setting of additional facility.

Extended release tablets can be prepared by compression of granules containing drug and release retarding polymer prepared by any of the following methods.

(i) Granulation
(ii) Hot fusion
(iii) Microencapsulation and compression
(iv) Pelletization and compression

The method used for preparing the controlled released drug delivery system of metoprolol tartrate is by granulation. Hence, this method is taken up for discussion.

6.7. GRANULATION

Most powders cannot be compressed directly into tablets because

(i) They lack the proper characteristics for binding or bonding together into compact entity and

(ii) They do not ordinarily possess the lubrication and disintegrating properties required for tabletting.

For these reasons, drugs must first be pretreated, either individually or in combinations usually with filler and other necessary components to form granules that tend themselves to tabletting. This process is known as granulation[27].

The reasons for granulation[28]

- Render the material free flowing.
- Densify materials.
- Prepare uniform mixtures that do not separate.
- Improve the compression characteristics of the drug.
- Control the rate of drug release.
- Facilitate metering or volume dispensing.
- Reduce dust.
- Improve the appearance of the tablet.

The principle methods of granulating pharmaceuticals may be classified into three main categories: wet processes, dry processes and other processes. In the wet granulation process, a granulating liquid is used to facilitate the agglomeration process. In the dry granulation process, dry powder particles may be brought together mechanically by compression into slugs or more frequently today, by roller compaction.

Table 6.1. Process used for granulation.

General Granulation Process	Specific Methodology
Wet	Wet Massing Fluid Bed Granulation Spray Drying Pan Granulation Extrusion & Spheronization
Dry	Roller Compaction Slugging
Other	Humidification Prilling Melt Pelletization

Although some or all these methods are used in the pharmaceutical industry, wet granulation has been and continues to be the most widely used agglomeration process.

6.7.1. Wet Granulation[30,31]

It is the oldest and most conventional method of making tablets. Although, it is the most labor-intensive and most expensive of the available methods, it continues to persists because of its versatility[32].

Granulation is any process of size enlargement whereby small particles are gathered together into larger, permanent aggregates to render them into a free-flowing state[33]. Size enlargement, also called agglomeration, is accomplished by same method of agitation in mixing equipment or by compaction, extrusion or globulation.

Wet granulation is the process in which a liquid is added to a powder in a vessel equipped with a type of agitation that will produce agglomerates or granules. The possibility of moistening powders with a variety of liquids, which also act as carriers for certain ingredients, thereby enhancing the granulation characteristics, have many advantages.

Fundamentals of Wet Granulation Technique

6.7.2. Binding Agent[34]:

Solution of the binding agent is added to the mixed powders with stirring. The powder mass is wetted with the binding solution until the mass has consistency of damp snow or brown sugar. If the granulation is over-wetted, the granules will be hard, requiring considerable pressure to form the tablets, and the resultant tablets may have a mottled appearance. If the powder mixture is not wetted sufficiently, the resulting granules will be too soft, breaking down during lubrication and causing difficulty during compression.

6.7.3. Granule Drying[34]:

In drying granulations, it is desirable to maintain a residual amount of moisture in the granulation. This is necessary to maintain the various granulation ingredients, such as gums, in hydrated state. Also, the residual moisture contributes to the reduction of the static electric charges on the particles. In the selection of any drying process, an effort is made to obtain uniform moisture content. In addition to the importance of moisture content in granulation, it's handling during the manufacture steps, the stability of the products containing moisture-sensitive active ingredients may be related to the moisture content of the products.

6.7.4. Sieving[34]:

After drying, the granulation is reduced in particle size by passing it through a smaller-mesh screen. Following dry screening, the granule size tends to be more uniform. For dry granulations the screen size to be selected depends on the diameter of the punch. For example, tablets of 7/16th inch and larger, use 12 mesh is suggested.

6.7.5. Lubrication:[32]

Commonly used lubricants include talc, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oils and polyethylene glycol (PEG). Most lubricants with the exception of talc, are used in concentrations below 1%. When used alone, talc may require concentrations as high as 5%. Poor selection or excessive amounts can result in waterproofing and/ or delayed dissolution of the drug substance.

The addition of proper lubricant is highly desirable if the material to be tabletted tends to stick to the punches and dies. Immediately after compression, most tablets have

the tendency to expand and will bind and stick to the side of the die. The choice of the proper lubricant will overcome this effectively.

The method of adding a lubricant to a granulation is important if the material is to perform its function satisfactorily. The lubricant must be divided finely by passing it through a 60–100 mesh nylon cloth onto the granulation (- bolted i.e., dusted through this nylon clothe over the granules, to eliminate small lumps as well as increase the covering power of the lubricant). The granules are gently tumble mixed to distribute the lubricant and without breaking them down to finer particles.

Many formulators once believed (and some still believe) that over-blending resulted in increased amounts of fines and hence, caused air entrapment in the formula. The capping and laminating of tablets associated with over-blending lubricants is thought to be caused by these air pockets. Most scientists now recognize that a plausible explanation has to be with the function of the lubricants themselves. Since the very nature of the lubricant tends to make surface less susceptible to adhesion, over-blending affects compaction.

Selection of Granule Sieve Fraction[34]:

It has been claimed that too much fine powder is not desirable because fine powder may not feed into the die evenly; consequently, variations in weight and density result. Fine powders, commonly designated as fines, also blow out around the upper punch and down past the lower punch, making it necessary to clean the machine frequently. Fines however at the level of 10 to 20%, traditionally are sought by the tablet formulator. The presence of some fines in necessary for the proper filling of the die cavity. The flow diagram involving typical steps in wet granulation is given in Fig.6.1.

6.7.7. Advantages of Wet Granulation

- The cohesiveness and compressibility of powders is improved due to the added binder that coats the individual powder particles, causing them to adhere to each other so that they can be formed into agglomerates called granules. Lower pressures are needed to compress tablets that enhances tool-life and decreases machine wears.

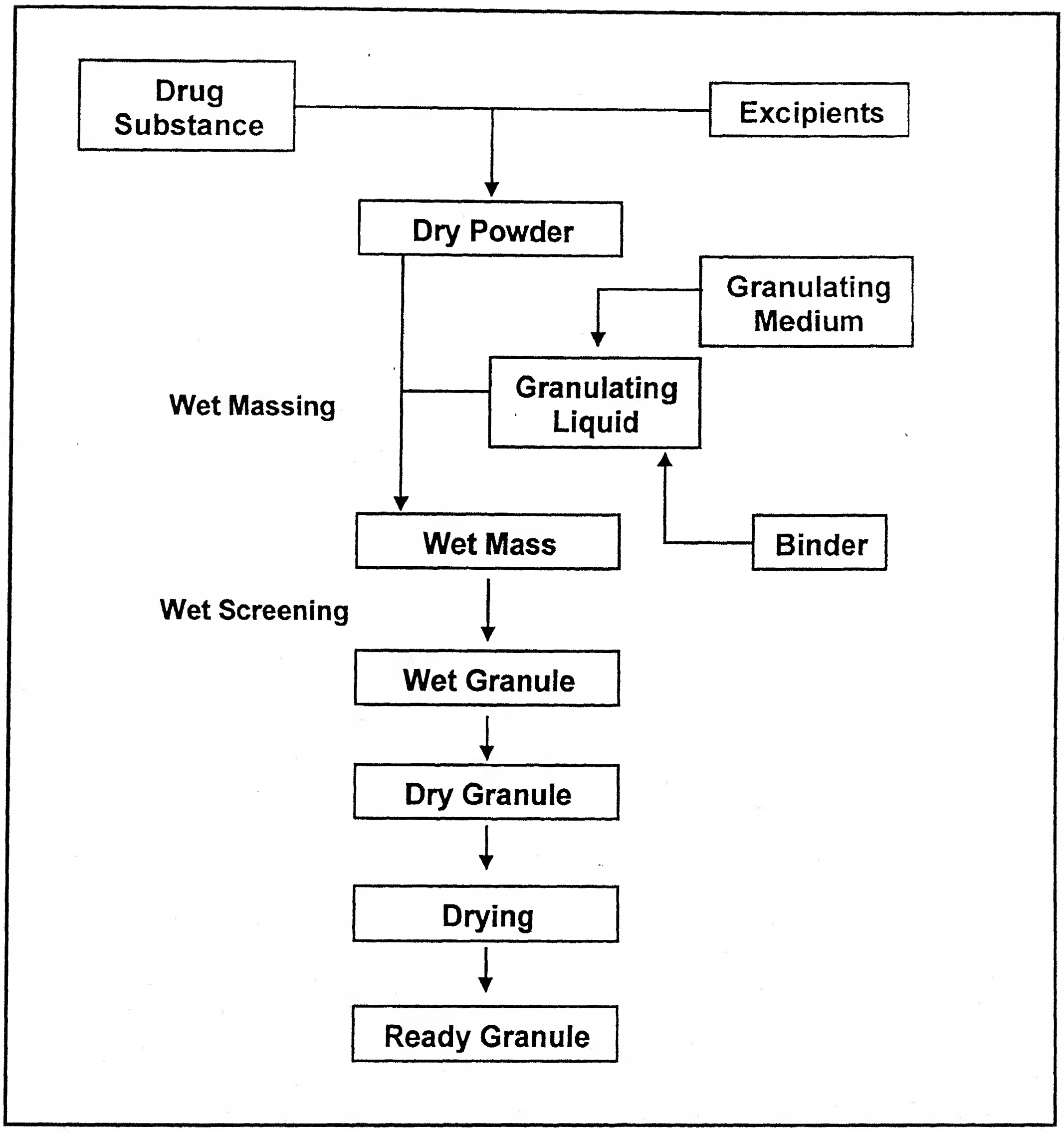

Fig.6.1. Processing steps in Wet Granulation.

- Drugs having a high dosage and poor flow and/or compressibility must be granulated by the wet method to obtain suitable flow and cohesion for compression.
- Good distribution and uniform content for soluble, low-dosage drugs and color additives are obtained if these are dissolved in the binder solution.
- A wide variety of powders can be processed together in a single batch.
- Bulky and dusty powders can be handled without producing a great deal of dust.
- Wet granulation prevents segregation of components of a homogeneous powder mixture during processing, transfer and handling.
- The dissolution rate of an insoluble drug may be improved by wet granulation with proper choice of solvent and binder.
- Controlled granulation can be accomplished by the selection of a suitable binder and solvent.

6.7.8. Limitations of Wet Granulation

- Because of the large number of processing steps, it requires a large area with temperature and humidity control.
- Requires a number of pieces of expensive equipment.
- Time consuming, especially the wetting and drying steps.
- Possibility of material loss during processing due to the transfer of material from one unit operation to another.
- Greater possibility of cross-contamination than with the direct-compression method.
- Presents material transfer problems involving the processing of sticky masses.
- Cannot be complete aqueous process, in case of hydrophilic polymer matrix.

During recent years some advances have been made to improve the traditional wet granulation method and reduce its cost. These include:

- Development of high precision automatic systems to determine the end point of the granulation process.
- Design of granulation units in which the whole process of solid-solid mix, liquid-solid kneading, and drying can be completed in one unit.
- Design of fluidized-bed granulators by adaptation of a spray nozzle to fluidized-bed dryers to add the binder. These systems are examples of control granulation to obtain uniform agglomerates. Granulation and drying are carried out simultaneously.
- Development of high speed or shearing mixtures, which provide efficient and quick solid-solid and solid-liquid blending, reducing time and material handling.
- Development of extrusion techniques as a special wet granulation method using more binder liquid and there the end product exhibits higher bulk density. Specific equipment is used because of different rheologic characteristics of the wet mass caused by higher wetting.
- A recent innovation in wet granulating, which reduces the time and energy requirements by eliminating the drying step, is the melt process. This method relies on the use of solids having a low softening or melting point which, when mixed with a powder formulation and heated, liquefy to act as binders[35-36]. Materials used as binders are polyethylene glycol 4000 and polyethylene glycol 6000[37-38], stearic acid[39], and various waxes[40-41].
- A new variation of the granulating process known as "moisture-activated dry granulation"[42] combines the efficiency of dry blending with the advantages of wet granulation. As little as 3% water produces agglomeration. The process requires no drying step because any free water is absorbed by the excipients used. After

granulation, disintegrant and lubricant are added and the granules are ready for compression[42-43].

6.8. TABLET COMPRESSION OPERATION

Tablets are made by compressing a formulation containing a drug or drugs with excipients on stamping machines called Tablet Compression Presses. Tablet machines are designed with the following basic components:

(i) Hopper for holding and feeding granulation to be compressed.

(ii) A feeding mechanism for moving granulation from the hopper into the dies.

(iii) Dies that define the size and shape of the tablet.

(iv) Punches for compressing the granulation within the dies.

Tablet presses are classified as either single punch or multi-station rotary presses. Single punch machine gives one compression per cycle. Since only upper punch is involved in the compression, tablets produced in these machines may have inferior uniformity of compactness. Multi-station presses are termed rotary because the head or turret of tablet machine that holds the upper punches, dies, and lower punches in place, rotates. As the head rotates, the punches are guided up and down by fixed cam tracks, which control the sequence of filling, compression, and ejection. Compared to single punch, the rotary presses are known for their high speed and better compaction. This is due to smoother movement of punches and involvement of both upper and lower punches in compression. Rotary machines also deliver tablets, which have better reliability and reproducibility. These machines are very versatile, and have been modified to produce various novel tablet forms such as dry coated, multi-layered and special delivery type dosages.

6.9. OPTIMIZATION

The optimization of pharmaceutical formulation with regards to one or more attributes has always been a subject of importance and attracts attention of those engaged in formulation research. Product formulation is often considered an art. The pharmaceutical scientist has, therefore, the responsibility to choose formulation whose attributes conform to certain predefined requisites. The word "optimize" is defined as "to make as perfect, effective or functional as possible"[45]. The word "optimization" is used in pharmacy with respect to standardization of formulation and to processing condition.

6.9.1. Optimization of Tablet Dosage Form

In extended release tablets as in conventional tablet formulation, optimization of all formulations and processing conditions is necessary to obtain an effective optimum product.

Optimization involves:

- Drug properties and excipients like particle size and distribution, crystal nature, bulk density and moisture content, to name a few. Type and concentration of excipients like retarding polymer, binders, lubricants etc.

6.9.2. Process and Equipment Optimization

- **Mixing:** Mixer type, mixing time, mixing speed, vessel capacity and load.
- **Drying:** Drying time, temperature, drying load, heat and air circulation in dryer, determination of cold spots, nature of inlet air in terms of quality, temperature, humidity, type of dryer (fluid bed dryer / tray dryer / infrared dryer etc.).
- **Lubrication:** Time of mixing, type of mixer. These have a profound effect on the disintegration and dissolution properties of the formulation.

- **Compression:** Hardness, flow through hopper, speed of compression, thickness of tablets, shape of tablets etc. Each of these has some say in either the availability of drug (hardness), content of drug in dosage form (flow through hopper) or in packing (thickness and shape).

Optimization studies in table granulation have been studied by many workers via factorial design using various aspects like (a) type of mixers viz., Diosna mixer and Planetary, indicated that impeller speed, the moisture content of starch and added amount of water; (b) in Fluid Bed Granulator – inlet air temperature, air volume, spray gun number, height from bed, atomization, air pressure, spray rate significantly influences the response variable, i.e., granule size and size distribution. They also found that drug concentration, excipient and binder, solvent nature; all influence the response variables. In controlled release formulation, optimization becomes much more critical as it may have drastic effects on drug release profile. In addition to the usual tablet properties, studies of pharmacokinetic parameters such as time to reach plasma concentration, lag time, absorption and elimination rate constants have also been optimized.

For the present work, tabletting by the process of wet granulation mixer was planned with an intension of optimization and scale up to product level.

6.9.3. Granules Evaluation

The granules produced after granulation are evaluated for appearance, loss on drying, particle size distribution, flowability and derived properties such as *Carr's* Index as per procedures reported in the chapter.

6.9.4. Tablet Evaluation

6.9.4.i. General Appearance[46]

The general appearance of a tablet, its visual identity and overall "elegance", is essential for consumer acceptance, for control of lot-to-lot uniformity and general tablet-to-tablet uniformity, and for monitoring trouble-free manufacturing. The control of the general appearance of the tablet involves the measurement of number of attributes such as tablet's size, shape, color, pressure or absence of odor, tastes, surface texture, physical flaws and consistency, and legibility of any identifying marking.

6.9.4.ii. Size & Shape[46, 47]

A compressed tablet's shape and dimensions are determined by tooling during the compression process. The thickness of a tablet is the only dimensional variable related to the process. The crown thickness of individual tablets may be measured with a micrometer, which permit accurate measurement and provides information on the variation between tablets. Tablet thickness can be controlled within ± 5% variation of a standard value. The physical dimensions of the tablet, along with the density of the materials in the tablet formulation and their proportions, determine the weight of the tablet.

6.9.4.iii. Unique Identification Markings

These markings utilize some form of embossing, engraving, or printing[45sir]. The type of informational markings placed on a tablet usually includes the company name or symbol, a product code, the product name, or the product potency.

6.9.4.iv Organoleptic Properties[46, 47-50]

- **Color:** The color of a product must be uniform within single tablet from tablet to tablet, and from lot to lot. Efforts to quantitate color evaluations have used reflectance spectrophotometry, trimulus colorimetric measurements, and the use of a microreflectance photometer to measure the color uniformity and gloss on a tablet surface. Many pharmaceutical tablets use colors as a vital means of rapid identification and consumer acceptance.
- **Odor:** Odor could be characteristic of the drug or formulation. But the presence of an off odor in a batch of tablets could indicate a stability problem, or could be characteristic of the drug in the dosage form.
- **Taste:** Taste is important in consumer acceptance of chewable and certain other tablets.

A tablet's level of flaws such as chips, cracks, contamination from foreign solid substances, surface texture and appearance may have a zero-defect specifications, but the visual inspection technique used for detecting or evaluating these characteristics are subjective in nature. Electronic devices that are currently being developed hold promise for making inspection a more quantitative and reproducible operation.

6.9.4.v. Mechanical Strength[51, 52-56]

The mechanical strength of a table is associated with the resistance of the solid specimen towards fracturing and attrition. An acceptable tablet must remain intact during handling between production and administration. This, an integral part of the formulation and production of tablets is the determination of their mechanical strength. Such testing is carried out for several reasons, such as:

(i) To assess the importance of formulation and production variables for the resistance of a tablet toward fracturing and attrition during formulation work, process design and scaling up;

(ii) To control the quality of tablets during production (in-process and batch control);

(iii) To characterize the fundamental mechanical properties of materials used in tablet formulations.

The most commonly used methods for strength testing can be subcategorized into two main groups: (i) attrition-resistance methods and (ii) fracture resistance methods.

Attrition-Resistance method: The idea behind attrition resistance methods is to mimic the kind of forces to which a tablet is subjected during handling between its production and its administration. These are also referred to as friability tests: a friable tablet is one that is prone to erode mechanically during handling. During handling, tablets are subjected to stresses from collisions and tablets sliding towards one another and other solid surfaces, which can result in the removal of small fragment and particles from the tablet surface. The result will be a progressive reduction in tablet weight and a change in its appearance. Such attrition can occur even though the stresses are not high enough to break or fracture the tablet into small pieces. Thus, an important property of a tablet is its ability to resist attrition so as to ensure that the correct amount of drug is administered and that the appearance of the tablet does not change during handling. Another application of a friability method is to detect incipient capping, as tablets with no visible defects can cap or laminate when stressed an attrition method, e.g., a rotation cylinder.

- Normally, weight loss of less than 1% during friability test is required. In addition, the tablets should not show capping or cracking during such testing.

Fracture resistance methods: Analysis of the fracture resistance of tablets involves the application of a load on the tablet and the determination of the force needed to fracture or break the specimen along its diameter. The force needed for fracture of a tablet depends on the tablets dimensions.

For a cylindrical flat-faced tablet, the tensile strength (σ_t) can be calculated by equation (6.12)

$$(\delta_t) = {}^{2F}\!/_{\pi D_t} \qquad (6.13)$$

where F is the force needed to fracture the tablet and D and t are the diameter and the thickness of the cylindrical flat-faced tablet, respectively

6.9.4.vi. Hardness

The tablets require a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacturing, packaging and shipping. In addition, tablets should be able to withstand reasonable abuse when in hands of the consumer, such as bouncing about in a woman's purse in a partially filled prescription bottle. Adequate tablet hardness and resistance are requisites for consumer acceptance[46].

6.9.4.vii. Friability[57]

For a tablet with a unit mass equal to or less than 650 mg, take a sample of whole tablets corresponding to 6.5 gm. For tablets with a unit mass of more than 650 mg take a sample of 10 whole tablets. Accurately weigh the tablet sample, and place the tablets in the drum. Rotate the drum 100 times, and remove the tablets. Remove any loose dust from the tablets as before, and accurately weigh.

- If obviously cracked, cleaved, or broken tablets are present in the tablet sample after tumbling, the sample fails the test. If the results are doubtful or if the weight loss is greater than the targeted value, the test should be repeated twice and the

mean of the three tests determined. A maximum weight of the tablets being tested is considered acceptable for most products. In the case of new formulations, an initial weight loss of 0.8% would be permitted until sufficient packaging data are obtained to extend the limit to a targeted value of 1%.

- If the tablet size or shape causes irregular tumbling, adjust the drum base so that the base forms an angle of about 10^{O} with the bench top and the tablets no longer bind together when lying next to each-other, which prevents them from falling freely.
- In case of hygroscopic tablets, humidity – controlled environment (relative humidity less than 40%) is required for testing.

6.9.4.viii. Disintegration[58]

This test is provided to determine compliance with the limits on Disintegration stated in the individual monograph except where the label states that the tablets or capsules are intended for use as troches or are to be chewed, or are designed as modified-release dosage forms.

- Disintegration does not imply complete solution of the unit or even of its active constituent. Complete disintegration is defined as that state in which any residue of the unit, except fragment of insoluble coating or capsule shell, remaining on the screen of the test apparatus is a soft mass having no palpably firm core.

6.9.4.ix. Uniformity of Dosage Units[59]

The uniformity of dosage units can be demonstrated by either of two methods, weight variation or content uniformity. And the relative standard deviation (RSD) was calculated using the formula

$$S = \left[\frac{\sum\left(x_i - \overline{X}\right)^2}{n-1}\right]^{\frac{1}{2}} \qquad (6.14)$$

and

$$RSD = \frac{100s}{\overline{X}} \qquad (6.15)$$

where s = sample standard deviation, RSD = relative standard deviation (the sample standard deviation expressed as a percentage of the mean), $\overline{X}$ = mean of the values obtained from the units tested, expressed as a percentage of the label claim/ strength of the formulation, n = number of units tested, x_1, x_2, x_3.... x_n = individual values (x_i) of the units tested, expressed as a percentage of the label claim/ strength of the formulation.

6.9.4.x. Weight Variation[59]

With a tablet designed to contain a specific amount of drug in a specific amount of tablet formula, the weight of the tablet being made, is routinely measured to help ensure that a tablet contains the proper amount of drug. In practice, a composite sample of tablets (usually 10) are taken and weighed throughout the compression process as in-process evaluation.

- The Pharmacopoeial weight variation test is done by usually weighing 20 tablets individually, calculating the average weight, and comparing the individual tablet weights to the average.
- To assure uniform potency of tablets of low dose drugs, a content uniformity test is applied.

6.9.4.xi. Drug Content and Release

As mentioned earlier, a physically sound tablet may not produce the desired effects. To evaluate a tablet's potential for efficacy, the amount of drug per tablet need to be monitored from tablet to tablet and batch-to-batch.

6.9.4.xii. *In vitro* Dissolution Testing

A biopharmaceutical[60] critical[61] test method to measuring the performance of the pharmaceutical products and is required by the Compendia. It is an important tool in quality control and an aid in developing pharmaceutical formulations. It measures changes in the stability of the product, and it establishes *in vitro – in vivo* correlations[61].

Pharmaceutical companies rely heavily on the *in-vitro* dissolution or release test to develop extended-release products and to ensure their performance *in vivo*. Wagner[62] stated, "future research in dissolution rates should be directed mainly towards establishing correlations of the *in vitro* data with the *in vivo* data". A strong correlation between the *in vitro* and the *in vivo* results can predict the *in vivo* performance accurately and therefore indicates the tests usefulness as a tool for development and production control. To reach a valid correlation, one has to have valid methods to yield meaningful measurement, both *in vitro* and *in vivo*, according to Extended Release Oral Dosage Forms: Development, Evaluation, and Application of *In vitro/In vivo* Correlations, US FDA[63].

6.9.4.xii.a. Objectives In Performing Dissolution Tests[60]

(i) Investigation of drug release mechanism, especially ER formulations.

(ii) To obtain a predefined target release profile and robust formulation properties regarding influences of physiological factors (e.g., pH and food) on the drug release.

(iii) Generation of supportive data to bioavailability studies as an aid in interpretation of *in vivo* results.

(iv) Validation of manufacturing process.

(v) Investigation of effects of different storage conditions.

(vi) Batch quality control (QC).

(vii) A surrogate for bioequivalence studies.

An *in vitro* dissolution method for batch QC is always defined for a new solid dosage form product. However, this method may not be sufficient for all the different aims of dissolution testing that might arise. The choice of dissolution method and test conditions should therefore be adapted to best serve their purpose. For example, simplicity and robustness are crucial properties of a QC method; whereas physiological relevance may overrule these factors when a method is used for *in vivo* predictions[60].

Standard *in vitro* dissolution testing models two process: (i) the release of drug substance from the solid dosage form and (ii) drug dissolution. Drug release will be determined by formulation factors such as disintegration/dissolution of formulation excipients or drug diffusion through the formulation. Drug dissolution will be affected by the physicochemical substance properties (e.g., solubility, diffusibility), solid-state properties of the substance (e.g., particle surface area. Polymorphism) and formulation properties (e.g., wetting, solubilization). *In vitro* dissolution testing should thus provide predictions of both the drug release and the dissolution process *in vivo*. Therefore, in most situations, the use of *in vitro* dissolution will be meaningless if the method used does not provide some correlation with the *in vivo* data or resemblance with the physiological conditions in the *g.i.t.* In order to reach this goal, the choice of dissolution apparatus and test medium should be carefully considered. Another important aspect in the development and definition of a new method is that it must be designed and operated in such a way that drug release and dissolution are not sensitive to minor variations in the operating conditions[60].

6.9.4.xii.b. Choice of Dissolution Apparatus[60]

The choice of dissolution apparatus will be specific for each formulation, and the following factors should be considered:

(i) Correlation to *in vivo* data.

(ii) Risk for hydrodynamic artifacts.

(iii) Regulatory guidelines.

(iv) Drug solubility.

(v) Need to change the dissolution medium during dissolution testing.

(vi) Ease of operation, in-house know-how and suitability for automation.

6.9.4.xii.c. Choice of Agitation Intensity[60]

All compendial dissolution apparatus can be operated at different agitation intensities. The three most outstanding aspects to consider when deciding at which level the test should be performed are

(i) Correlation to the *in vivo* data

(ii) Variability of dissolution results

(iii) Regulatory Guidelines and Pharmacopoeial Recommendations.

The US regulatory agency recommends a stirring rate of 50-100 rpm, for USP I and 50-75 rpm for USP II.

6.9.4.xii.d. Choice of Dissolution Test Media[60]

The choice of the dissolution medium is highly dependent on the purpose of the dissolution study, but the following aspects should always be considered

(i) Correlation to *in vivo* data.

(ii) Resemblance of physiological conditions in the *GI* tract.

(iii) Regulatory and Pharmacopoeial recommendations.

(iv) Drug solubility and stability properties – at different pH values.

(v) Known sensitivity of the formulation function for different medium factors.

Attainment of *IVIVC* is a key aspect in the choice of dissolution test medium. However, it is recommended to choose a test medium based only on correlation to *in vivo* data. The dissolution test medium should also be relevant for the physiological conditions in the *GI* tract. Another important aspect is selection of sink conditions.

6.9.4.xii.e. Controlled Release Workshop Recommendations for In vitro Tests:

The Controlled Release Workshop[64] recommends that the *in vitro* test is desirable for the purpose of (i) providing necessary process control and stability determinations of the relevant release characteristics and (ii) Facilitating certain regulatory determinations and judgments, concerning minor formulation changes, site of manufacturing changes, etc. It recommended:

A. Preparation of at least three dosage formulations with different biopharmaceutic characteristics (change in *in vitro* dissolution of these test dosage forms being accomplished by changing only these process and component variables that are likely to be varied under normal manufacturing conditions;

B. Development of an appropriated *in vitro* test capable of distinguishing between these formulations; characteristics of these formulations in a small group of human subjects. The *in vitro* drug release kinetics of the dosage form intended to be marketed should be characterized as a function of medium pH, rate of agitation, and possibly also medium composition (such as surfactants and bile salts). Since the knowledge of controlled release product IVIVC development and testing is still evolving, alternative approaches to this problem should be explored and should be considered by the Agency on their merits.

The key elements for dissolution are: (i) Reproducibility of the method, (ii) proper choice of media, (iii) maintenance of sink conditions, (iv) control of solution hydrodynamics, (v) dissolution rate as a function of pH ranging from pH 1 to pH 8, including several intermediate values, preferably as topographic dissolution characterization, (vi) selection of the most discriminating variables (media, pH, rotation speed, etc.) as the basis for the dissolution test and specifications.

C. The dissolution procedure should establish (i) Lack of dose dumping – indicated by a narrow limit on the one hour dissolution specifications, (ii) Controlled release characteristics – by employing additional sampling windows over time (Narrow limits with an appropriate Q value system will control the degree of first order release), (iii) Complete drug release – indicated by a 75 – 80 % minimum release specification at the last sampling interval and (iv) and dosage form pH dependence/independence indicated by percent dissolution in water, appropriate buffer, gastric (minus enzyme) and simulated (minus enzyme) fluid.

6.9.4.xii.f. Biopharmaceutical Classification System for Drugs

Amidon et al[65] devised a biopharmaceutical classification system (BCS) to classify drugs on their aqueous solubility and intestinal permeability. It was then recognized that dissolution rate has a negligible impact on bioavailability of highly soluble and highly permeable (BCS I) drugs when their formulations dissolution is sufficiently rapid[66]. As a result, various regulatory agencies including the US FDA now allow bioequivalence of formulations of BCS Class I drugs to be demonstrated by *in vitro* dissolution (often called a biowaiver)[67, 68].

The principles of *in vitro* drug release can be extended to other dosage forms where the product sameness can be ensured by profile comparison between[69]. In addition, *in vitro* dissolution/drug release test can also be used for providing *biowaivers* for low strengths of a product from a given manufacturer, once the higher strength is approved based on the appropriate *bioavailability/bioequivalence* test procedure[70].

6.9.4.xii.g. Guidelines And Compendial Specifications

The Division of Bio-Equivalence (DBE) in the Office of Generic Drugs (OGD), FDA, issued a guidance[71], "Oral extended (controlled) release dosage forms: *In vivo bioequivalence* and *in vitro* dissolution testing". The bio-studies and dissolution testing required to support an ANDA for an ER product are discussed in detail in Section IV. In addition to biostudies and dissolution data, the following are significant:

(i) Although the generic product and the listed reference product must be pharmaceutically equivalent, the mechanism by which the release of active substance occurs does not have to be same.

(ii) The biobatch used for *in vivo bioequivalence* studies must conform to the OGD Policy and Procedure Guide 22-90[72].

(iii) The assay potencies of the test and reference products should not differ by more than 5 %.

(iv) A single dose, two-way cross over fasting study is required for each strength of a generic ER tablet product. The multiple dose, steady state study and the food study are conducted only on the highest strength.

(v) A single dose, two way crossover fasting study is required for only the highest strength of a generic extended release capsule product, provided that: (a) formula compositions of the lower strength are proportional to that of this highest strength and (b) the capsule contains identical beads or pellets.

Single-dose studies for the lower strengths may be waived on the basis of acceptable dissolution testing. The multiple dose and food studies are to be conducted with the highest strength of the capsule formulation.

A workshop report on controlled/modified release dosage forms[73] was issued regarding "*In vitro* and *In vivo* Testing and Correlation for Oral Controlled/Modified Release Dosage Forms," and recommendations were made concerning which pharmacokinetic studies were needed in several cases. Case III is for generic equivalents of approval extended release products. The generic formulation must be comparable with respect to rate and extent of availability (using the parameters AUC, C_{max} (peak concentration), C_{min} (trough concentration and fluctuation) to the standard extended release product in a steady-state crossover study. The food studies as described in Case I are also needed. The workshop report also agreed in principle with the USP article on IVIVC[74] but recognized that separate correlations may be required for each manufacturer's extended release product. The *in vitro* dissolution method and specifications must be optimized for response to the range of critical manufacturing variables that affect drug release. FDA describes how to apply similarity factor (f_2 calculation) to compare dissolution profiles of different batches to assess or establish bioequivalence[75-77].

Dissolution test is provided to determine compliance with the dissolution requirements where stated in the individual monograph for a tablet or capsule dosage form. Where the label states that an article is enteric coated, and a dissolution or disintegration test that does not specifically state that it is to be applied to enteric-coated articles is included in the individual monograph, the test for *Delayed Release Articles* under *Drug Release*[78] is applied unless otherwise specified in the monograph. For hard or soft gelatin capsules and gelatin – coated tablets that does

not conform to the Dissolution specifications, repeat the test as follows. Where water or medium with a pH of less than 6.8 is specified as the *Medium* in individual monograph, the same *Medium* specified may be used with the addition of purified pepsin that results in an activity of 7,50,000 Units or less per 1000 mL. For media with a pH of 6.8 or greater, pancreatin can be added to produce not more than 1750 USP Units of protease activity per 1000 mL.

6.9.4.xii.h. Drug Release[78]

This test is provided to determine compliance with drug – release requirements where specified in individual monographs. Use the apparatus specified in the individual monograph. Replace the aliquots withdrawn for analysis with equal volumes of fresh *Dissolution Medium* at 37 ^{o}C or, where it can be shown that replacement of volume change in the calculation. Keep the vessel covered for the duration of the test, and verify the temperature of the mixture under test at suitable times.

For ER products labeled to be administered every 12-24 hour, the sampling schedule is: 1 and 2 hour, to ensure lack of dose dumping; 4hour, to establish extended release characteristics; every 2 hour, to establish at least 80 % release. If the release is less than 80 %, dissolution conditions should be changed. In general, the range of release a each sampling time should not exceed 30% with ranges of 20-25% preferred by DBE Specifications for drug release are determined on a case-by-case basis[79].

6.9.4.xii.i. Criteria for Acceptance Level[78]

The individual monograph requirement are met if the quantities of active ingredient (Q) are dissolved from the units tested conform to Acceptance Table 1, shown below.

Table 6.2. Official specification for *In vitro* dissolution acceptance level for extended release tablets[78].

Level	Number Tested	Criteria
L_1	6	No individual values lies outside the stated ranges and no value is less than the stated amount at the final test time.
L_2	6	The average value of the 12 units (L_1+L_2) lies within each of the stated ranges and is not less than the stated amount at the final test time; none is more than 10 % of the label content outside each of the stated ranges; and none is more than 10 of labeled content below the stated amount at the final test time.
L_3	12	The average value of the 24 units (L_1+L_2+L_3) lies within each of the stated ranges, and is not less than the stated amount at the final first time; not more than 2 of the 24 units are more than 10 % of labeled content outside each of the stated ranges; not more than 2 of the 24 units are more than 10 % of the labeled content below the stated amount at the final test time; and none of the units is more than 20 % of the labeled content outside each of the stated ranges or more than 20 % of the labeled content below the stated amount at the final test time.

6.9.4.xii.j. Reference Listed Drug[81]

The US FDA Center for Drug Evaluation and Research (CDER), Glossary of Terms, Reference Listed Drug (RLD) defines (CDER, Glossary) as an approved drug product to which new generic versions are compared to show they are bioequivalent. A drug company seeking approval to market a generic equivalent must refer to the RLD in its Abbreviated New Drug Application (ANDA). By designating a single reference drug as the standard to which all generic versions must be shown to be bioequivalent, FDA hopes to avoid possible significant variations among generic drugs and their brand name counterpart.

6.10. SCALE UP OF FORMULATION[82]

Scale up is generally defined as the process of increasing the batch size. Scale up of a process can also be viewed as a procedure for applying the same process to

different output volume. In moving from lab scale to production scale it is sometimes essential to have an intermediate batch size. This is achieved at the so-called pilot scale, which is defined as the manufacturing drug product by a procedure fully representative of and simulating that is used for full manufacturing scale. For a successful scale up a large amount of information on the process during development has to be generated, key parameters need to be identified. Many scale up parameters are non-linear. Process characterization and verification is must for scale up. Robust formulation is prerequisite for scale up.

6.10.1. Scale Up Consideration For Granulation

Granulation or size enlargement of primary particles is carried out in variety of ways. Various mechanisms of granule formation have been described in literature to summarize three mechanisms for granule formation:

- Bridges due to immobile liquid form adhesional and cohesional bridging bonds. Thin adsorption layer bonding of fine particles under circumstances.
- Mobile liquids, where interfacial and capillary forces are present.
- Solid bridges formed due to crystallization of dissolved substances drying.

During scale up, the quality of the granules is essential. A change in granule size distribution, final moisture content, friability, compressibility and compactibility may have a strong influence on the properties of final tablet such as hardness, friability, disintegration, dissolution.

Various equipments have been used for wet granulation. Out of these mixer/kneader high shear/ low shear and fluid bed granulator are commonly used.

In case of mixer/ kneader, the granulation process can be easily monitored by monitoring power consumption. Key factor here is correct amount and type of granulating liquid. Interpretation of power consumption plots can also be important for optimizing granulation liquid quantity and type. The wet granules are then dried for removal of moisture or solvent usually in fluid bed or tray driers. Drying involves heat and mass transfer. Heat is transferred to the product and mass is transferred as moisture to surrounding gas, and these two phenomena are independent. This free moisture is amount of moisture that can be removed from material by drying at specified temperature and humidity. The amount of moisture that remains associated with material under drying conditions specified is called the equilibrium moisture content (EMC). Therefore, drying air capacity, air distribution through the product is key to drying process and its scale up. Relative humidity and temperature of inlet air have influence on drying air capacity.

6.10.2. Scale Up Consideration For Tabletting

Two important variables such as formulation variables and equipment variables are to be considered during scale up of tabletting process. Material properties such as free flowing, cohesiveness, lubrication - needs to be evaluated for successful scale up batch. Laboratory test such as particle size analysis, bulk density, angle of repose, funnel flow time are used to compare properties of the scale batches.

Tablet properties useful for evaluation of scale up process; tablet weight and hardness; thickness; friability; assay; uniformity of dose, dissolution. Tablet hardness and dissolution are very important.

Moore et al[83] have described a mathematical model describing similarity factor, f_2. Mathematical fit factor f_2 has been accepted by US FDA for comparison of dissolution.

$$f_2 = 50.\log[1 + (1/n)\Sigma \mid R_j - T_j \mid^2 . 100] \qquad (6.16)$$

where R_j = % drug release of reference product at each time point j

T_j = % drug release of test product at each time point j

n = sampling number

Calculation of Similarity factor, f_2 based on the dissolution points on two curves one of each of two products is important. A similarity factor value between 50 and 100 indicates that the two profiles are similar.

6.11. DRUG RELEASE MECHANISMS AND MODELLING[84]

The quantitative analysis of the values obtained in dissolution/release tests is easier when mathematical formulas that express the dissolution results as a function of some of the dosage forms characteristics are used. In some cases, these mathematic models are derived from the theoretical analysis of the occurring process. In most of the cases the theoretical concept does not exist and some empirical equations have proved to be more appropriate. Drug dissolution from solid dosage forms has been described by kinetic models in which the drug dissolved amount of drug *(Q)* is a function of the test time, *t*, or Q = *f(t)*. Some analytical definitions *of* the *Q(t)* function commonly used are zero order, first order, *Hixson-Crowell*, *Higuchi* and *Korsmeyer-Peppas* models. Other release parameter such as, difference factor (f_1) and similarity factor (f_2) are used to characterize drug release profiles.

6.12. STABILITY TESTING

The term "stability" with respect to a drug dosage form refers to the chemical and physical integrity of the dosage unit to maintain protection against microbial contamination. The shelf life of the dosage form is the time lapse from initial preparation to the specified expiration date. The monograph specifications of identity, strength, quality, and purity apply through out the shelf life of the product[85].

6.12.1. Routes by which pharmaceuticals degrade

6.12.1.i. Chemical Degradative Routes

- **Solvolysis[86-87]:** In this type of reaction the active drug undergoes decomposition following reaction with the solvent present.

- **Oxidization[89-91]:** In pharmaceutical dosage forms, oxidation is usually medicated through reaction with atmospheric oxygen under ambient conditions – a process commonly referred to as oxidation. Many auto-oxidation reactions are initiated by trace amounts of impurities, such as metal ions or hydroperoxides.

- **Photolysis[92-94]:** Normal sunlight or room light may cause substantial degradation of drug.

- **Dehydration[95-97]:** Since it is possible that anhydrous compounds may have different dissolutions rates compared with their hydrates, dehydration reactions involving water of crystallization may potentially affect the absorption rates of the dosage form.

- **Racemization**[97-98]: Enantiomers often have significantly different absorption, distribution, metabolism, and excretion; in addition to differing pharmacological actions.

- **Incompatibilities**[99]: Chemical interactions frequently occur between two or more components in the same dosage form, or between active ingredient and a pharmaceutical adjuvant, in pharmaceutical formulation.

- **Other chemical degradation reactions**[100]: Hydration, decarboxylation, pyrolysis, etc.

6.12.1.ii. Physical Degradative Routes

- **Polymorphs**[101-104]: Polymorphs may exhibit significant differences in important physiochemical parameters, such as solubility, dissolution rate and melting point.

- **Vaporization**[105-106]: Some drugs and pharmaceutical adjuvants possess sufficiently high vapor pressure at room temperature at room temperature that their volatilization through the package component constitutes a major route of drug loss.

- **Ageing**[107-110]: The most interesting and perhaps the least-reported area of concern about the physical instability of pharmaceutical dosage forms, is generally termed as ageing. In as ER formulation containing a relatively stable drug like lithium salt, consideration of ageing is of prime importance. This is a process through which changes in the degradation or dissolution characteristics of the dosage form are caused by subtle and sometimes unexplained, alterations

in the physicochemical propertied of the inert ingredients or the active drug in the dosage form. Since the disintegration and dissolution steps may be the rate determining steps in the absorption of a drug, changes in these process, as a function of the "age" of the dosage form, may result a corresponding changes in the bioavailability of the drug product. This is of special significance in ER release dosage forms. Ageing of solids forms can cause a decrease in their *in vitro* rate of dissolution, and a corresponding decrease in *in vivo* absorption cannot be assumed automatically.

- **Adsorption[111-112]:** It is a drug-plastic interaction, which is increasingly being recognized as a major physical problem.

6.12.2. Stability Testing in Pharmaceutical Industry[113]

The ICH Q1A R Stability Testing Guidelines: Stability Testing of New Drug Substances and Products, The European Agency for Evaluation of Medicinal Products Evaluation of Medicines for Human Use, November 2000 is revised version of the ICH Q1A guideline and defines the stability data package for new drug substance or drug product that is sufficient for a registration application within the three regions of EC, Japan, and United States.

The guideline addresses the information to be submitted in registration application for new molecular entities and associated drug products. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test period for the drug substance or shelf life for the drug product and recommended storage conditions.

- **Stress Testing:** Stress testing of the drug substance can help identify the likely degradation products, which can in turn help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual drug substance and the type of drug product involved. Stress testing is likely to be carried out on a single batch of the drug substance.

- **Selection of Batches:** Data from formal stability studies should be provided on at least three primary batches of the drug substances. The batches should be manufactured to a minimum of pilot scale by the same synthetic route as, and procedure that stimulates the final process to be used for, production batches. The overall quality of the batches of drug substances place on formal stability studies should be representative of the quality of the material to be made on the production scale.

- **Container Closure System:** The stability studies should be conducted on the drug substances packaged in a container closure system that is the same as or simulates the packaging proposed for storage and distribution.

- **Testing Frequency:** For long-term studies, frequency of testing is normally every 3 months over the first year, every 6 months over the second year, and annually thereafter. At the accelerated storage conditions, a minimum of three times points, including the initial and final time points (e.g., 0, 3, and 6 months), from a 6-month study is recommended.

- **Storage Conditions:** Long term, accelerated, and where appropriate, intermediate storage conditions for drug substances are given below.

Table 6.3. Storage Conditions[90].

Study	Storage conditions	Minimum time period
Long term	$25^{o}C \pm 2^{o}C/60\%$ RH $\pm$ 5% RH	12 months
Intermediate	$30^{o}C \pm 2^{o}C/60\%$ RH $\pm$ 5% RH	6 months
Accelerated	$40^{o}C \pm 2^{o}C/75\%$ RH $\pm$ 5% RH	6 months

"Significant Change" for a drug substance is defined as failure to meet specifications.

6.12.3. Climatic Zones[114-118]

As per many authors, the real life climatic conditions should be considered while selecting the stability testing criteria. It was reported that either unsafe drug products reach market or more often than not stable drugs are necessarily discarded. In many countries like USA, the term "controlled room temperature" is used to describe temperatures in the 15- 30^{o}C range prevailing in such diverse thermostatically maintained environments as pharmacies, hospitals and warehouses. While designing the product, it appears to be important to identify the climatic conditions prevailing at the place of destination and consumption. For this purpose, the world has been divided into four climatic zones (Table 6.4) to one of which various places of different countries can be assigned.

Table 6.4. Climatic Zones.

Zone	Climatic Zone Definition	Storage Conditions
I	Temperate Climate	21^{o}C / 45% RH
II	Subtropical & Mediterranean Climate	25^{o}C / 60% RH
III	Hot, Dry Climate	30^{o}C / 35% RH
IV	Hot, Humid Climate	30^{o}C / 65% RH

6.12.4. Official Stability Considerations[119]

Each ingredient, whether therapeutically active or pharmaceutically necessary, can affect the stability of drug substances and dosage forms. The primary environmental factors that can reduce stability include exposure to adverse temperatures, light,

humidity, oxygen and carbondixode. Five types of stability recognized are shown in the table below:

Table 6.5. Criteria for acceptable level of stability[119].

Type of Stability	Conditions Maintained throughout the Shelf-life of the Drug Product
Chemicai	Each active ingredient retains its chemical integrity and labeled potency, within the specified limits.
Physical	The original physical properties including appearance, palatability, uniformity, dissolution, and suspendability are retained.
Micobiological	Sterility or resistance to microbial growth is retained according to the specified requirements. Antimicorbial agents that are present retain effectiveness within the specified limits.
Therapeutic	The therapeutic effect remains unchaged.
Toxicological	No significant increase in toxicity occurs.

6.12.5. Program

- **Scope and Goals:** Activities encompassed by the stability program include sample storage of development or production batches, data collection and storage retrieval; physical, chemical and microbiological testing; document preparation for regulatory submission, and package evaluation.

- **Protocols:** FDA Guidelines and ICH Guidelines are detained concerning sampling, storage conditions and specific test parameters for each dosage form. Accelerated testing is generally done more frequently and for a short duration. Generally, real-time data obtained at the label storage conditions on the final formulation in the final packaging configurations are needed for a NDA.

- **Documentation:** the need for adequate documentation of laboratory operations is established not by good science, but also by regulatory requirement.

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Chapter 7

Materials
&
Method........

7.A. MATERIAL

7.A.1. ACTIVE DRUG SUBSTANCE – METOPROLOL TARTRATE

The active substance MT is suitable candidate for formulation in CDDS[1]; administered in 100 to 450 mg daily, in divided doses[2]. The elimination half-life is about 3-7 hours in most patients and is independent of the dose and duration of therapy[3]. The drug is readily and completely absorbed from the *g.i.t.* Peak plasma concentrations vary widely and occur about 1.5 to 2 hours after single oral dose. It belongs to Class 1[4-5] based on Biopharmaceutical Classification System (BCS) based on solubility in aqueous media and intestinal permeability.

The free gift sample was obtained from AstraZenca Limited Bangalore, which had following batch details mentioned for the active drug MT.

Product	Metoprolol Tartrate
Batch No.	MTB AO 58
Manufacturing Date	May/2000
Expiry Date	April/2005
Assay	99.18%

Table 7.1. Pharmacopoeial Specifications for Metoprolol Tartrate[6].

Test parameter	Compendia Limits
Description	White, crystalline powder or colorless crystals
Identification	Infrared Absorption
Melting point	121 –124 ^{O}C
pH	6.0 - 7.0 (in 2.0% w/v solution).
Clarity & color of solution	A 2.0% w/v solution is clear.
Specific optical rotation	(+) 7.0^{O} – (+) 10.0^{O} at 20^{O} in 2.0% w/v solution.
Heavy metals	Not more than 10 ppm.
Sulphated ash	Not more than 0.1%.
Loss on drying	Not more than 0.5% determined on 1 gm by drying in an oven at $105^{O}C$.
Chromatographic purity	Not more than RS spot.
Assay (titrimetry)	Between 99.0 -101.0 % of $(C_{15}\text{-}H_{25}NO_3)_2.C_4H_6O_6$.

7.A.2. CONTROL RELEASE POLYMER – HPMC K4M and HPMC K100M

Free gift samples of hydroxypropyl methyl cellulose (HPMC) K4M and HPMC K100M were obtained from Colorcon Asia Pvt. Ltd., Charkop, Kandivali(W), Mumbai 400 0677. The manufacturer (Colorcon Asia Pvt. Ltd.) claims that its manufactured product meets the requirement of the USP-23 and European Pharmacopoiea 3rd Ed. and is certified Kosher. The product specifications are given in Table 7.2.

7.A.2.1. Dow® Safety Data Sheet[7-8]

The material safety details provided by The Dow Chemical Company for the product HPMC K4M and K100M PREM are:

i. Product Name

METHOCEL* K4M/ or K100M PREMIUM HYDROXYPROPYL METHYLCELLULOSE EP (i.e., minimum 95 % < 100 mesh screen) GRADE.

ii. COMPOSITION/INFORMATION ON INGREDIENTS

Modified cellulose

iii. HAZARDS INDENTIFICATION

This product is not hazardous according to EC criteria.

iv. FIRST-AID MEASURES

Never give fluids or induce vomiting if patient is unconscious of is having convulsion.

- Inhalation: Remove to fresh air if effects occur. Consult a physician.
- Skin Contact: Wash off in flowing water or shower.
- Eye Contact: Irrigate immediately with water for at least 5 minutes.
- Ingestion: Consult a physician who will decide on need and method of emptying stomach.

Table 7.2. Hydroxypropyl methylcellulose product specifications as given by the manufacturer[9-10].

Details	Polymer Type	
	Methocel K4M	Methocel K100M
Batch Number	NJ21012N12	NE14012NO2
Date of Manufacture	October 2000	August 2000
Drug Mfg. Lic. No.	1234	1234
Test Item	**Specifications**	
Description	White to slightly off white, fibrous or granular powder.	White to slightly off white, fibrous or granular powder.
Identity	Meets the requirements of the USP and PhEUR.	Meets the requirements of the USP and PhEUR.
Appearance of solution	Less colored than reference solution Y_6 and less opalescent than reference suspension III.	Less colored than reference solution Y_6 and less opalescent than reference suspension III.
pH (1% solution)	5.5 –8.0	5.5 –8.0
Methoxy content	19.0-24.0%	19.0-24.0%
Hydroxypropoxyl content	7.0-12.0%	7.0-12.0%
Apparent viscosity	2308-3755 mPa.s (nominal value 2903 mPa.s by rotation)	16922-19267 mPa.s (nominal value 18243 mPa.s by rotation)
Apparent viscosity	3000-5600 cP (nominal value 4000 cP by Ubbelhode)	80000-120000 cP (nominal value 100000 cP by Ubbelhode)
Chlorides	Maximum 0.5%	Maximum 0.5%
Heavy metals	Maximum 10 ppm as Pb	Maximum 10 ppm as Pb
Loss on drying	Maximum 5.0%	Maximum 5.0%
Sulphated Ash	Maximum 1.0%	Maximum 1.0%
Organic Volatile Impurities	Will pass USP test <467>	Will pass USP test <467>
Particle Size	Minimum 99.0% through No 40 US standard sieve.	Minimum 99.0% through No 40 US standard sieve.
Packaging	25 Kg polylined fibre drums.	25 Kg polylined fibre drums.
Storage	The recommended storage temperature is 5-35 ^{O}C.	The recommended storage temperature is 5-35 ^{O}C.
	Stability and Reactivity	
Chemical Stability	Stable under normal handling and storage conditions.	Stable under normal handling and storage conditions.
Materials to avoid	Oxidizing agents.	Oxidizing agents.
The material has a recommended shelf life of five years from the date of manufacture if stored in closed container.		

v. FIRE-FIGHTING MEASURES

- Extinguishing media: Water fog or fine spray. Carbon dioxide.
- Extinguishing media to Avoid: DO NOT USE WATER JET. Dust explosion hazard may result from forceful application of fire extinguishing agents.
- Hazardous Combustion Products: None known. Complete combustion will give carbon dioxide and water.
- Protection of Firefighters: Wear positive-pressure self-contained breathing apparatus and protective fire fighting clothing (includes fire fighting helmet, coat, trousers, boots and gloves).
- Specific Fire or Explosion Hazards: Dust of this product suspended in air is flammable and poses a definite explosion hazard if ignited.

vi. ACCIDENTAL RELEASE MEASURE

- Methods to Cleaning up: Sweep up, recover if possible, or dispose of according to applicable regulations. Spills may cause very slippery surfaces when wet. If the spill is a viscous solution it should be further diluted with water before disposal.

vii. HANDLING AND STORAGE

- Handling: Fine dust of this product can form explosive mixture with air and poses a definite fir and explosion hazard at all times; keep away from ignition sources. May cause very slippery surfaces when wet. The minimum dust explosion concentration is 30-160 g/m^3.
- Storage: The recommended storage temperature is 5-35 ^{O}C.

viii. EXPOSURE CONTROLS/ PERSONAL PROTECTION

- Exposure Guidelines: The UK Health and Safety Executive has established an Occupational Exposure Standard (OES) of 10 mg/m^3 8-hour TWA total inhalable dust and 5 mg/m^3 8-hour TWA respirable dust.

- Engineering Controls: Good general ventilation should be sufficient.
- Personal Protective Equipment:
  - Respiratory Protection: No respiratory protection should be need.
  - Skin Protection: No precautions other than clean body-covering
  - clothing should be needed.
  - Eye/Face Protection: Use safety glasses.

ix. PHYSICAL AND CHEMICAL PROPERTIES

- Appearance: powder
- Color: white to off-white
- Odor: none
- Boiling point/range: not applicable
- Freezing point/range: not applicable
- Vapour pressure: swells in water; no solubility limit
- Relative vapour density (air=1): not applicable
- Specific gravity: not applicable
- pH: not applicable
- Log P (octanol/water): not applicable
- Flash point: not applicable
- Auto-ignition temperature: >350 ^{O}C
- Flammability: not applicable

x. STABILITY AND REACTIVITY

- Chemical Stability: Stable under normal handling and storage conditions.
- Materials to Avoid: Oxidizing agents.

xi. TOXICOLOGICAL INFORMATION

- Ingestion: Single dose oral toxicity is considered to be low. The oral LD_{50} for rats is >2000mg/kg.
- Skin Contact: Essentially non-irritating to skin. Skin absorption is unlikely due to physical properties.

- Eye Contact: Essentially non-irritating to eyes. Solid or dust may cause irritation or corneal injury due to mechanical action.
- Inhalation: No adverse effects are anticipated from inhalation.
- Other information: Based on available data, repeated exposures are not anticipated to cause significant adverse effects.

xii. ECOLOGICAL INFORMATION

- Degradation: Biodegradation under aerobic conditions is below detectable limits. Despite the very slow biodegradation rate the product should not present any environmental hazard in the water/soil compartment.
- Aquatic Toxicity: Modified celluloses are generally non-harmful to aquatic organism ($LC_{50}/EC_{50}/IC_{50}$ greater than 100mg/L).

xiii. DISPOSAL CONSIDERATIONS

Any disposal practice must be in compliance with all local and national laws and regulations. Customers are advised to check their local legislation on governing the disposal of waste materials.

xiv. TRANSPORT INFORMATION

Product is not classified for any mode of transportation.

xv. REGULATORY INFORMATION

EC Classification and User Label Information

xvi. OTHER INFORMATION

No other information.

7.A.2.2. Particle Size Distribution of HPMC (Sieve Analysis)[11-12]

Particle size of polymer can greatly influence polymer performance in the hydrophilic matrix Fractions of polymers with smaller particle size have more surface area

relative to equivalent weights of fractions with larger particle size. The greater surface area provides for better polymer-water contact, thus increasing the overall rate at which complete polymer hydration and gelation occurs. This leads to more effective formation of the protective gel barrier so critical to the performance of hydrophilic matrix tablets. Hence, particle characterization of the polymer by sieve analysis was undertaken.

7.A.3. DILUENT – LACTOSE MONOHYDRATE (General Reagent Grade)

The product was purchased from Loba Chemicals, Mumbai. The specifications given on the container were

i. Molecular Formula: $C_{12}H_{22}O_{11}.\ H_2O$

ii. Molecular Weight: 360.31

iii. Mfg. By: Loba Chemie

iv. Batch No.: 56897

Total Water Content: 4.8 – 5.4%

Maximum limits of impurities

i. Free acid – limit 0.25 mL N%

ii. Insoluble matter: 0.005%

iii. Alcohol soluble impurities: 0.2%

iv. Nitrogen compounds (N): 0.02%

v. Arsenic (As): 0.001%

vi. Copper (Cu): 0.00005%

vii. Iron (Fe): 0.0002%

viii. Lead (Pb): 0.00005%

(Alcohol soluble impurities. For bacteriological purpose. Free from glucose)

7. A.4. LUBRICANT – MAGNESIUM STEARATE

(precipitated fine powder, General Reagent Grade)

The product was purchased from Loba Chemicals, Mumbai. The specifications given on the container were

i. Molecular Formula: $C_{36}H_{70}MgO_4$

ii. Molecular Weight: 591.27

iii. Mfg. By: Loba Chemie

iv. Batch No.: 57168

v. Assay of Magnesium (calculated on dry substance): 4.5%

vi. Ash: 7.5%

vii. Loss on drying (105 ^{O}C): 3.5%

viii. pH (saturated solution): 6.2 – 7.4

ix. Heavy metals (as Pb): 0.002%

x. Zinc stearate: 0.5%

xi. Chloride (Cl): 0.02%

xii. Sulphate (SO_4): 0.2%

xiii. Acid number of precipitated fattyacid: 195 - 210

7. B. METHODS

7. B.1.PREFORMULATION STUDIES

7. B.1.1. Spectral Scan of Active Drug Substance

The UV absorption spectrum of active substance MT in distilled water was performed to determine the spectrum peaks using 2 nm bandwidth Jasco V-530 UV-Spectrophotometer. A suitable quantity of MT was dissolved in distilled water and the spectrum measurement of the sample was performed against distilled water as the solvent reference blank. The scanning range was set 200-1000 nm at a speed, 40 nm/min and the data-collecting wavelength was 0.1 nm, with 3-cycle number.

Note: Any sample subjected for spectral absorption, during the entire period of experimental work was filtered using Millipore Millex-HV 13mm filter unit consisting of PVDF membrane filter with a pore size rating of 0.45 µm, so as eliminate any suspended impurities interfering with the studies.

7. B.1.2. Melting Point

Melting point was determined as per IP 1996 method. The results both determined and taken from the literature are included.

7. B.1.3. pH

A 2% solution of MT distilled water was used to determine the pH using calibrated pH meter.

7. B.1.4. Dissociation Constant (*pKa*)

The values for MT reported in the literature taken.

7. B.1.5. Moisture Content

Samples of MT (0.2 gm) were subjected to determination of their moisture content using Karl Fischer Titrimeter (AutoTirt..tor, Labindia, Mumbai) using specially dried methanol (E. Merck, India) and combined Karl Fischer Reagent (E. Merck, India).

7. B.1.6. Density and Flowability

The samples (10 gms) of MT were subjected to evaluation of bulk density and tap density using a calibrated measuring cylinder (25 mL, Borosil) and Bulk Density Apparatus (Campbell Electronics, India) respectively; flowability was obtained from angle of repose obtained using funnel technique. Derived powder characteristics such as Bulkiness, *Carr's* Compressibility Index and *Hausner's* Ratio were calculated using standard equations described in detail in Chapter 6.

7. B.1.7. Drug-Excipient Compatibility Studies

7. B.1.7.i. Fourier transform infra red spectroscopic (FTIR)[10]

For the consistent, reliable, and safe development of drug products, FTIR spectra were obtained to characterize pharmaceutical solids at the molecular level for complete characterization of materials used in the development of extended release formulation containing MT.

Method: The pre-dried (3 hours at 60 ^{o}C) samples were taken in the ratio of ~1:100 sample to KBr; triturated in the agate mortar with the pestle and placed on the holder. Spectra were obtained by diffuse reflectance technique using KBr on Jasco FT/IR –460 Plus with a resolution set for 4 cm^{-1} and with a scanning speed of 2mm/sec over a wavelength of 4000 to 400 nm over the data gathered after 16

accumulation (repeats). The base line correction for KBr was performed and corrected for the sample.

7. B.1.7.ii. Chromatographic Studies

The drug polymer compatibility test was further analyzed by Chromatographic technique after storage under accelerated conditions of temperature and humidity (50 ^{O}C and 70% RH for 3 weeks)[13]. The samples were powder-blended and compressed in the tablet machine to get the hardness of 8 kg/cm^2 (to simulate tabletting); used in the study. The USP 27[14] modified method was used for analysis of the sample. In place of Thin Layer Chromatographic Plate, Paper was used (Whattman Chromatographic Paper) and rest of the procedure remained the same. The details of which are stated below:

(i) The Test Solutions of drug MT and the mixtures of drug and polymer HPMC K4M, K100M, diluent Lactose and lubricant magnesium stearate were prepared in 90% ethanol, for spotting.

(ii) Chromatographic Chamber was lined with absorbent paper, and poured into the chamber containing 250 mL of a mixture of chloroform, methanol, ammonium hydroxide (80:15:2); the chamber was allowed to saturate for 1.5 hours.

(iii) About 5-μL portions of the Test Solution was applied at a distance of 2.5 cm from the bottom of the paper, the spots were dried and the paper was suspended in the Chromatographic chamber, closed the chamber, and allowed the chromatogram to develop until the solvent front moved about three-fourths of the length of the chromatogram. The chromatogram was removed, dried in a current of warm air until the odor of ammonia was no longer perceptible (about 45 minutes).

(iv) A beaker containing 0.5 gm of potassium permanganate was placed in the chamber and then 5 mL of 6 N hydrochloric acid was added to the beaker;

allowed to equilibrate for 5 minutes. Then the chromatogram was placed in the chamber for five minutes and then removed. The chromatogram was allowed to stand in a current of cool air for 1 hour before it was sprayed with detecting reagent.

(v) For detecting reagent, the solutions of potassium iodide (1 in 100) and soluble starch (prepared by triturating 3 gm in 10 mL of cold water and adding the mixture to 90 mL of boiling water with constant stirring) was prepared. Just prior to use, mixed 10 mL of each solution with 3 mL of alcohol.

- **Evaluation of Chromatogram**

For the evaluation of the chromatogram, the number of spots and the R_f values were studied. R_f value is defined as the ratio of distance traveled by the solute to the solvent front and is characteristic for a particular substance under given set of eluting conditions.

$$R_f = \frac{\text{(Distance traveled on the medium by the compound)}}{\text{(Distance traveled by the front of the mobile phase)}}$$

Increase in number of spots means there the mixture has undergone degradation and change in R_f values indicate some chemical changes occurring in the substance under analysis. However, if the R_f value remains the same for the pure drug and the drug in the mixture(s), then it indicates the drug in particular mixture is compatible.

7.B.2. STANDARD CALIBRATION CURVE

7.B.2.1. General Introduction[15]

Test procedures used for the assessment of various quality levels of different batches were strived to be in line with the Compendia. It consisted of the following sections (i) Rationale, (ii) Analytical Procedures and (iii) Data Elements, as described in USP.

Rationale: This section should identify the need for the method and describe the capability of the specific method proposed and why it is preferred, a comparison should be provided of limitations of the current Compendial method and advantages offered by the proposed.

Proposed Analytical Procedure: This section should contain a complete description of the analytical method sufficiently detailed to enable persons "skilled in the art" to replicate it. The write-up should include all important operational parameters and specific instructions such as preparation of reagents, performance of systems suitability tests, description of blanks used, precautions, and explicit formulas for calculation of test results.

Data Elements: This section should provide thorough and complete documentation of the validation of the analytical method. It should include summaries of experimental data and calculations substantiating each of the applicable analytical performance characteristics. These characteristics are described in the following Sections.

Validation: Validation of an analytical method is the process by which it is established, by laboratory studies, that the performance characteristics of the method meet the requirements for the intended analytical application. Typical analytical performance characteristics that should be considered in the validation of the types of method described in this document are (1) Accuracy, (2) Precision, (3) Specificity, (4) Detection Limit, (5) Quantitation Limit, (6) Linearity and (7) Range.

7.B.2.2. Analytical Performance Characteristics[15]

Accuracy (definition): The accuracy of an analytical method is the closeness of test results obtained by that method to the true value. The accuracy of an analytical method should be established across its range.

- Accuracy is calculated as the percentage of recovery by the assay of the known added amount of analyte in the sample, or as the difference between the mean and the accepted true value, together with confidence intervals.
- The ICH documents recommend that accuracy should be assessed using a minimum of nine determinations over a minimum of three concentration levels, covering the specified range (i.e., three concentrations and three replicates of each concentration).

Precision (definition): The precision of an analytical method is the degree of agreement among individual test results when the method is applied repeatedly to multiple samples of a homogeneous sample.

- The precision of an analytical method is usually expressed as the standard deviation or relative standard deviation (coefficient of variation) of a series of measurements.
- Precision may be a measure of either the degree of reproducibility or of repeatability of the analytical method under normal operating conditions.

In this context, reproducibility refers to the used of the analytical procedure in different laboratories as in a collaborative study. Intermediate precision expresses within – laboratory variation as on different days, or with different analysts or equipment within the same laboratory.

Repeatability refers to the use of the analytical procedure within a laboratory over a short period of time using the same analyst with the same equipment.

- For most purposes, repeatability is the criterion of concern in USP analytical procedures, although reproducibility between laboratories or intermediate precision may well be considered during the standardizing of a procedure before it is submitted to the Pharmacopoeia.

- The ICH documents recommend that repeatability should be assessed using a minimum of nine determinations covering the specified range for the procedure (i.e., three concentrations and three replicates of each concentration or using a minimum of six determinations at 100% of the test concentrations.

Specificity (definition): The ICH documents define specificity as the ability to assess unequivocally the analyte in the presence of components that may be expected to be present, such as impurities, degradation products, and matrix components. Lack of specificity of an individual analytical procedure may be compensated by other supporting analytical procedure.

Detection Limit (definition): The detection limit is a characteristic of limit tests. It is the lowest amount of analyte in a sample that can be detected, but not necessary quantitated, under the stated experimental conditions.

Quantitation Limit: The quantitation limit is a characteristic of quantitative assays for low levels of compounds in sample matrices, such as impurities in bulk drug substances and degradation products in finished pharmaceuticals. It is the lowest amount of analyte in a sample that can be determined with acceptable precision and accuracy under the stated experimental conditions. The quantitation limit is expressed as the concentration of analyte (e.g., percentage, parts per billion) in the sample.

Linearity: The linearity of an analytical method is its ability to elicit test results that are directly, or by a well-defined mathematic transformation, proportional to the concentration of analyte in samples within a given range.

Range: The range of an analytical method is the interval between the upper and lower levels of analyte (including these levels) that have been demonstrated to be determined with a suitable level of precision, accuracy, and linearity using the

method as written. The range is normally expressed in the same units as test results (e.g., percentage, parts per million) obtained by the analytical method.

Determination of Linearity and Range: Linearity should be established across the range of the analytical procedure. It should be established initially by visual examination of a plot of signals as a function of analyte concentration of content. If there appears to be linear relationship, test results should be established by appropriate statistical methods (e.g., by calculation of a regression line by the method of least square). In some cases, to obtain linearity between the response of an analyte and its concentration, the test data may have to be subjected to a mathematical transformation. Data from the regression line itself may be helpful to provide mathematical estimates of the degree of linearity. The correlation coefficient, y-intercept, slope of the regression line, and residual sum of squares should be submitted.

- The range of the method is validated by verifying that the analytical method provides acceptable precision, accuracy and linearity when applied to samples containing analyte at the extremes of the ranges as well as with the range.
- ICH recommends that, for the establishment of linearity, a minimum of five concentrations normally be used. It is also recommended that the following minimum specified range should be considered.

ASSAY OF DRUG SUBSTANCE (or a finished product): from 80% to 120 5 of the test concentration.

DETERMINATION OF AN IMPURITY: 50 - 120% of the specification.

FOR CONTENT UNIFORMITY: A minimum of 70% to 130% of the test concentration, unless a wider or more appropriate range, based on the dosage form (e.g., metered-dose inhalers) is justified.

FOR DISSOLUTION TESTING: ± 20% over the specified range, based on the specifications for a controlled-release product cover a region from 20%, after 1 hour, and upto 90%, after 24 hours, the validated range would be 0% to 110% of the label claim.

Ruggedness: The ruggedness of an analytical method is the degree of reproducibility of test results obtained by the analysis of the same samples under a variety of conditions, such as different laboratories, different analysts, different instruments, different lots of reagents, different elapsed assay times, different assay temperatures, different days, etc. ruggedness is normally expressed as the lack of influence of test results of operational and environmental variables of the analytical method. Ruggedness is a measure of reproducibility of test results under the variation in conditions normally expected from laboratory to laboratory and from analysts to analysts.

Robustness: The robustness of an analytical method is a measure of its capacity to remain unaffected by small but deliberate variations in method parameters and provides an indication of its reliability during normal use.

7.B.2.3. Spectral Scan of Active Substance

The UV absorption spectrum measurement of active substance MT in pH 6.8-phosphate buffer was performed to determine the spectrum peaks using 2 nm band-width Jasco V-530 UV-Spectrophotometer. A suitable quantity of MT was dissolved in pH 6.8 phosphate buffer and the spectrum measurement of the sample was performed against pH 6.8-phosphate buffer as the solvent reference blank. The scanning range was set between 200 to 1000 nm at a speed of 40 nm/min and the data-collecting wavelength was 0.1 nm, with 3-cycle number.

Note: Any sample subjected for spectral absorption, during the entire period of experimental work was filtered using Millipore Millex-HV 13mm filter unit consisting of PVDF membrane filter with a pore size rating of 0.45 μm, so as eliminate any suspended impurities interfering with the studies.

7.B.2.4. Standard Calibration Curve (CC) of Metoprolol Tartrate

A suitable quantity of MT was accurately weight[16] using Afcoset Electronic Balance (sensitivity ± 0.1 mg so that measurement uncertainty (random plus systematic error) did not exceed 0.1% of the reading. The drug was dissolved in 100.0 mL pH 6.8-phosphate buffer to obtain the Stock Solution (SS). Aliquots of SS were suitably diluted with pH 6.8-phosphate buffer, to get series of MT. The spectrophotometric absorbances were determined at 275 nm against pH 6.8-phosphate buffer as the reference blank. Each sample measured was set to 10 cycles, at an interval of 5 seconds and with medium response. The Standard CC was obtained by plotting a graph of drug concentration versus absorbance. The statistical linear regression coefficient (slope), constant (intercept) and correlation coefficient values. The experiment was repeated for another 5 times and the corresponding data, linear regression values were calculated. From these replicated studies, the standard deviations were estimated.

7.B.2.5. Absorption Stability of Metoprolol Tartrate

During a particular analysis of the active drug, the analysis could for some reasons might not get completed immediately, but later on the next day. This might affect the UV spectral absorption values, if the active substance is prone to degradation in the medium. Hence the spectral absorbance stability of MT; at the same concentration was done over a period of 3 days in pH 6.8 phosphate buffer for 72 hours at 275 nm λ_{max} against pH 6.8 phosphate buffer as the blank. The percent deviation of change in the absorbance as a function of time was determined, for 6 sets.

7.B.3. ANALYTICAL METHOD AND ITS VALIDATION FOR METOPROLOL TARTRATE EXTENDED RELEASE TABLETS

Analytical grade reagents and distilled water was used through out the experimentation unless otherwise specified.

7.B.3.1. Preparation of Standard Solution

MT Reference Standard (RS) (99.18%), an accurately weighed quantity (60mg) of MT was dissolved in distilled water and diluted suitably to get the final drug concentration of 250 µgm/mL.

7.B.3.2. Preparation of Sample Solution

Twenty tablets were accurately weighed and their average weight was obtained. The tablets were finely crushed and powder equivalent to average weight of tablet was transferred to 100 ml conical flask and 30 ml of distilled water was added to it. The suspension was sonicated for about 30 mins followed by addition of water to make up the volume. The filtered portion of this solution (Millipore Membrane filter, 0.45µm) was used for spectral analysis.

7.B.3.3. Method validation

Excipient mixture (25 gm) without drug was prepared for use as placebo.

7.B.3.3.i. Accuracy

Accuracy of the analytical method was established by spiking MT RS (98.18%) on to the placebo. Accuracy was ascertained in three and over five concentration levels ranging between 135 µgm/mL and 410 µgm/mL (50-150% of drug concentration). MT tablets (average weight 250mg) contain drug and excipients (200mg). Accurately weighed drug (27-75 added to mg) was added to 30 mg powdered placebo tablets, mixed and transferred to 100 mL conical flask, 30 mL distilled water was added to it.

It was sonicated for about 30 mins followed by addition of distilled water to make up the volume. Filtered portions were taken for UV absorbance against distilled water as blank. Standard drug solution was prepared as described earlier Section 7.B.3.1 and its UV absorbance was taken.

Amount of MT (mg) was calculated using the following formula:

Amount of Metoprolol Tartrate = (T_A/S_A) .W_S. (P_S/10)

where T_A = absorbance of Test Solution

S_A = absorbance of Standard Solution

W_S = weight of Standard (mg)

P_S = potency of Standard

% Recovery = (amount found/amount added) 100

7.B.3.3.ii. Precision of Assay

Precision of assay of the tablet was carried out using six determinations in three sets (two sets on one day and third on next day) at 100% of the test concentration (i.e., 280 µgm/mL). Procedure for standard and sample preparation was as reported above. UV absorbance of these solutions was taken at 275 nm on UV Spectrophotometer using water as blank.

Amount of MT was estimated using the formula:

Amount of Metoprolol Tartrate = (T_A/S_A) .W_S. (P_S/10)

where T_A = absorbance of Test Solution

S_A = absorbance of Standard Solution

W_S = weight of Standard (mg)

P_S = potency of Standard

% Label Claim = (amount obtained (mg)/Label Clain) 100

7.B.3.3.iii. Ruggedness for *in vitro* dissolution data

Ruggedness for dissolution (n=6) was carried out in the same laboratory, on different days, with different formulations (check, pp 215). The dissolution was carried out on USP Apparatus Type II with 500 mL of dissolution medium; the temperature of the bath maintained at 37 ^{O}C ± 0.5 ^{O}C with paddle rotating at 50 rpm. Aliquots (10 mL) were withdrawn after time intervals of 1, 4 and 8 hours respectively and replenished with fresh medium maintained at 37 ^{O}C ± 0.5. The filtered aliquots were measured spectrophotometrically to estimate the amount of drug released against medium as blank. Standard solutions were prepared as described in Section 7.B.3.1 and UV absorbance taken.

7.B.3.3.iv. Specificity

Specificity of the method was established by analyzing samples containing placebo and other without placebo thereby demonstrating the ability of the Method to yield reliable results without any interference of placebo. UV scan of (i) Placebo and (ii) Placebo and Standard MT drug, were recorded in the range of 200 to 350 nm. Standard preparation with Placebo was prepared by adding accurately weighed amount of MT (99.18%, 50mg) to 30 mg powdered placebo in 100 mL volumetric flask, 30 ml distilled water was added to it. The resulting solution was sonicated for about 30 mins., the volume was made up with distilled water. The filtered portions of the solution were taken for UV –absorbance against distilled water as blank at 275 nm. Standard preparation without placebo was prepared as described in Standard Solution preparation above.

Amount of MT (mg) was estimated using the formula:

$$\textbf{Amount of Metoprolol Tartrate} = (T_A/S_A) . W_S . (P_S/10)$$

where T_A = absorbance of Test Solution

S_A = absorbance of Standard Solution

W_S = weight of Standard (mg)

P_S = potency of Standard

$$\% \text{ Agreement} = \frac{\text{Test results with placebo}}{\text{Test results without placebo}} .(100)$$

7.B.3.3.v. Limit of Detection (LOD) and Lin... of Quantification

UV scans of standard drug solutions (conc. < 5 µgm/mL) and the medium blank were recorded in the range of 200 to 400 nm. LOD was found to be 1µgm/mL having the absorbance of 0.0036. Limit of Quantification was found to be 6µgm/mL (6 times of the detection). Linearity at 50% and 150% of limit of Quantification Level (6µgm/mL) was carried out. The results of concentration against absorbance were plotted.

7.B.3.3.vi. Linearity and Range

Linearity of MT was carried out in the range of 25 µgm/mL to 300 as reported in Section 7.B.2.4. UV absorbance of the solutions was taken at 275 nm on UV spectrophotometer using pH 6.8 phosphate buffer solution as blank. The experiment was repeated six times. Plot of concentration against absorbance is drawn. After establishing linearity levels, range of the method was validated by verifying at the extremes of the range 25–300 µgm/mL.

7.B.4. LAB. SCALE FORMULATION AND FABRICATION OF ER DDS OF METOPROLOL TARTRATE – BY TABLETTING

(Wet-Granulation and Compression under High Pressure)

Taking into consideration drug-excipient compatibility studies, galenical development trials of extended release matrix tablets of MT employing wet granulation were undertaken with batch size of 50 gms. The fundamental principles of tablet manufacturing process have changed very little over the years[17]. Essentially an ctive is grouped up with binders, granulated, and then compressed to form a tablet[18-19].

7.B.4.1. Processing Steps

7.B.4.1.i. Sifting

All the materials (polymer, drug and excipients – lactose monohydrate and magnesium stearate) were passed through sieve # 80 mesh screen so that the particle size of each kind were approximately of same size[20].

7.B.4.1.ii. Dry Mixing /Blending

The drug, polymer, diluent and ½ of lubricant were blended by tumble-mix in a beaker for 20 minutes till the mixture was uniform (the method was standardized at the initial stage by scooping a sample of powder mass and then analyzing the amount of drug spectrophotometrically. The procedure was kept uniform for all the batches to minimize the error).

7.B.4.1.iii. Granulation

The pre-sieved powder mass is moistened with 90% V/V alcohol as a binder[21] to render it coherent but by no means wet. It is then passed through a # 14 mesh screen and the material sifted to obtain granules.

- Level of Solvent: The amount of solvent employed was such that the mass was merely moist (rather than wet or pasty). 90% v/v ethanol was used as a granulating agent. Once the granulating liquid was added, mixing was continued until uniform dispersion is attained (~1 minute). The end point of mixing was determined by pressing a portion of the mass in the palm of the hand; and if the ball crumbled under the moderate pressure, then the mixture was ready for the next stage.

7.B.4.1.iv. Drying

The wet granules were dried at a temperature not exceeding 60 ^{O}C ± 2 ^{O}C for 2 hours till loss on drying (LOD) of the granules was less than 5% determined gravimetrically.

- Drying was done to remove the solvent that is used in forming the aggregates and to reduce the moisture content within the granules.

7.B.4.1.v. Millling and Shifting

The dried granules were passed sifted through sieve # 20. The granules retained were milled in glass mortar with the help of pestle and passed through # 20. LOD of granules was determined by gravimetric method. The percentage of granules below sieve # 60 (% fines) were determined.

7.B.4.1.vi. Lubrication

Magnesium stearate was bolted over the granules and tumbled mixed for uniform distribution.

7.B.4.1.vii. Compression

The lubricated granules were compressed on 16-station D-tooling single rotary compression machine (make) using single set of punch and die with each batch granules weighed to 250mg, except for the optimized batch. The pressure was so adjusted to obtain tablet hardness of ~ 5 kg/cm^2 determined 1 hour after tabletting. A flow diagram of wet granulation process in hydrophilic tablet is shown in Fig 7.1.

- **Note:** All the operations were carried out in a dehumidified area at a relative humidity of less than 20% at 25 ^oC[17].

7.B.4.2. Formulation of ER Matrix Compressed Tablets

Initially, formulation variables were designed based on the clues obtained from the literature (details in Chapter 5 and 6). This involved three stages:

(i) 6 batches: A-1, A-2, A-3, A-4, A-5 and A-6 with low density HPMC K4M polymer at 5, 10, 20, 30, 40 and 50% concentration (w.r.t. total tablet weight).

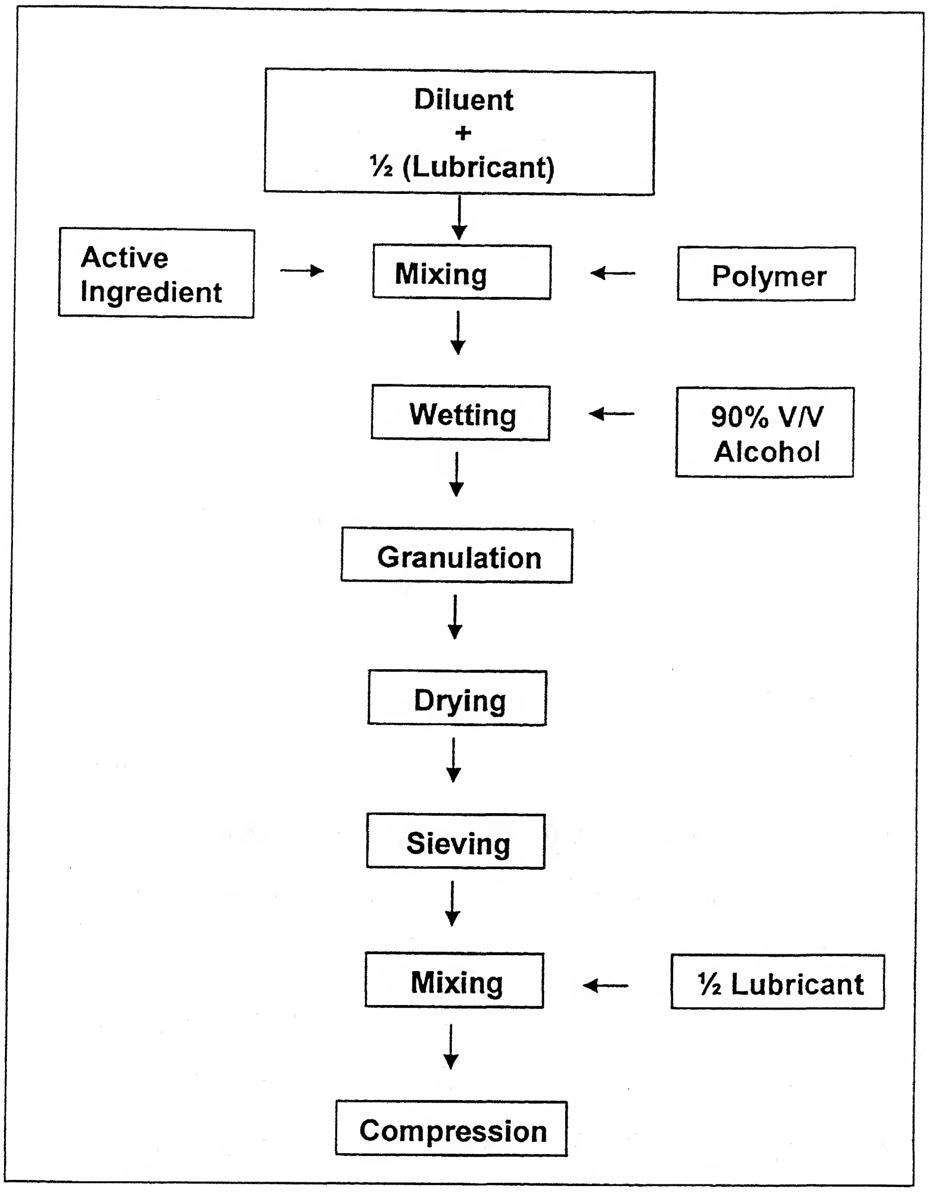

Fig. 7.1. The wet granulation process of hydrophilic matrix tablet preparation.

(ii) 3 batches: B-1, B-2 and B-3 with high density HPMC K100M polymer at 30, 40 and 50 % concentration (w.r.t. total tablet weight).

(iii) 2 batches: C-1 and C-2 using blends of HPMC K4M and HPMC K100M at 20:30 and 30:20 (at 50% concentration level w.r.t. total tablet weight).

- Concentration of drug MT was kept constant to 50 mg in all the formulations. The lubricant magnesium stearate was added at 1% of the tablet weight and the filler

lactose monohydrate was used to make up to constant weight of the tablet to 250 mg.

- A total of 11 batches were prepared with the drug. Placebo tablets were compressed without the drug for each batch.

7.B.4.2.i. Justification for Batch Design

- Initially, the low density polymer concentration was gradually increased (from 5 to 50% at 6 levels) to know the polymer concentration level required to obtain desired *in vitro* drug release profile for the material chosen.
- Based on the analysis of results obtained from the earlier batch studies, it was desired to vary the polymer concentration to only 3 effective concentration levels, to study the effect of molecular weight on the drug release, within the purview of defined objective.
- Lastly, it was thought to study the polymers blend for: **(a)** its effect on *in vitro* drug release profile; and **(b)** its possible implication and a way to control batch reproducibility in this type of formulations which uses the rheological properties governing the drug release mechanism from the dosage form. This thought was based on: (i) polymers are characterized with their average molecular weights, (ii) no two batches of polymer is in molecular weight and its solution properties, (iii) molecular weight of polymer is directly related to polymer rheological properties and thixotropy, (iv) the drug release from non-disintergrating controlled release matrix is mostly governed by two phenomena namely (a) drug diffusion rate of from the swollen matrix and (b) polymer erosion rate of gelled matrix. Rather going for one polymer, if polymer-blend is used, it would give better flexibility, control and reproducibility over the critical properties controlling the drug release properties. However, no experiments were undertaken to testify this theoretical analogy. The mathematical relationship describing viscosity for the polymer blend can be obtained using the following equation

$$(\eta_B)^{1/8} = F_1(\eta_1)^{1/8}\eta + F(\eta_1)^{1/8}$$

where F_1 and F_2 are weight fractions of polymer 1 and 2, η_1 and η_2 are viscosity of polymer 1 and 2 respectively.

The equation that expresses the approximate relationship between polymer solution viscosity and polymer concentration is

$$\eta = (1 + KC)^8$$

where η is the solution viscosity in mPa.s, C is the polymer concentration in solution (expressed in percent), and K is a constant specific to molecular weight.

7.B.4.2.ii. Justification for Batch Selecting a Batch for Lab. Pilot Scale Up and Further Studies

The USP 27 NF 22, 2004 Edition specifies the qualifying limits for Metoprolol as ER dosage form. Hence, from the prepared batches which had this qualifying *in vitro* release profile under specified *in vitro* dissolution test conditions. With the foregoing object the problem for optimized batch could be well defined expecting to have come to arrive at.

Defining the Problem

Make a controlled release tablet, which would not release more than 25 % of drug at the end of 1 hour and not less than 80 % at the end of 20^{th} hour and between 20-40 % at 4^{th} hour and between 40-60% at 8^{th} hour under specific dissolution conditions. Mathematically, it can be stated as:

"Amount of drug dissolved =

$T_{1\ hour} \geq 25$ %, $T_{4th\ hour}$ = 20-40%, $T_{8th\ hour}$ = 40-60%, $T_{20th\ hour} \leq 80$ %"

Table 7.3. Batch formula for the controlled release hydrophilic matrix delivery system of metoprolol tartrate

Formulation Code	Each 250 mg ER Matrix Tablet contains* (weight in mg)				
	Metoprolol Tartrate	**HPMC (K4M)**	**HPMC (K100M)**	**Lactose Monohydrate**	**Magnesium Stearate**
A-1	50 (20%)	12.5 (5%)	-	185.0 (74%)	2.5 (1%)
A-2	50 (20%)	25 (10%)	-	175.5 (70.2)	2.5 (1%)
A-3	50 (20%)	50 (20%)	-	147.5 (59%)	2.5 (1%)
A-4	50 (20%)	75 (30%)	-	122.5 (49%)	2.5 (1%)
A-5	50 (20%)	100 (40%)	-	97.5 (39%)	2.5 (1%)
A-6	50 (20%)	125 (50%)	-	72.5 (29%)	2.5 (1%)
B-1	50 (20%)	-	75 (30%)	122.5 (49%)	2.5 (1%)
B-2	50 (20%)	-	100 (40%)	97.5 (39%)	2.5 (1%)
B-3	50 (20%)	-	125 (50%)	72.5 (29%)	2.5 (1%)
C-1	50 (20%)	50 (20%)	75 (30%)	72.5 (29%)	2.5 (1%)
C-2	50 (20%)	75 (30%)	50 (20%)	72.5 (29%)	2.5 (1%)

* 10% overages (metorprolol tartrate) were added during granulation.

7.B.5. EXTENDED RELEASE TABLET EVALUATION

7.B.5.1. Tests As Described Earlier

The compressed ER matrix DDS were evaluated for (i) shape & color, (ii) size, (iii) friability, (iv) hardness, (v) weight variation, (vi) content uniformity. Details of which are already discussed in Chapter 3, Section 3.3. Further, (vii) disintegration and (viii) in vitro drug release tests were also performed.

7.B.5.2. Disintegration Test (DT) Method

By virtue of its non-disintegrating hydrophilic matrix form, these system show controlled release over time. Hence, in place of distilled water, pH 6.8 phosphate

buffer was used as the test medium. At every time interval (0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10 and 24) the basket assembly was lifted to observe the tablets. The time was recorded when there was no mass left on the screen and the time was recorded as DT time. The other parameters remain as described in Section 3.3 of chapter 3.

7.B.5.3. *In Vitro* Dissolution Studies

Compendial Test Conditions For ER Metoprolol Succinate

In USP 27, there is an addition of drug release test for Metoprolol Succinate ER dosage form (pp 1230-1231). The test specifications are:

- **Test Specifications**

  Dissolution Medium: 500 mL pH 6.8 phosphate buffer.

  Apparatus 2: 50 rpm

  Temperature: 37 ^{o}C (±0.5)

  Time: 1, 4, 8 and 20 hours

- **Analytical method for the estimation of drug released**

  Determine the amount of $(C_{15}H_{25}NO_3)_2\ C_4H_6O_4$ dissolved by employing HPLC method.

- Tolerance limits are given below:

Time (hours)	Amount Dissolved
1	Not more than 25%
4	Between 20% and 40%
8	Between 40% and 60%
20	Not less than 80%

Not less than 75% (Q) of the labeled amount $(C_{15}H_{25}NO_3)_2\ C_4H_6O_6$ is dissolved in 30 mins.

- Criteria for Acceptance Level[V19]: The individual monograph requirement is met if the quantities of active ingredient (Q) are dissolved from the units tested conform to Acceptance Table, given in Section **6.9.4.xii.i.**, Chapter 6.

- **Experimental Test Conditions For Metoprolol Tartrate**

  The laboratory experimental test conditions for developed ER formulations of metoprolol tartrate salt, based on above guidelines were set which are as follows:

- **Test Conditions**

Equipment:	Electrolab TDT-08L Dissolution Tester, USP, Mumbai.
Medium:	500 mL pH 6.8 phosphate buffer.
Apparatus 2:	50 rpm
Temperature:	37 ^{o}C (±0.5)
Time:	0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10 and 24 hours = 17 readings.
Aliquot withdrawn:	10 mL and replaced with same quantity of dissolution medium maintained at the same temperature.

- **Analytical method for the estimation of drug released**

  Spectrophotometric method was used instead of HPLC. The method used is described in section 7.B.2.4.of this chapter. The amount of drug released is estimated using the slope value of standard calibration curve of MT at 275 nm.

7.B.6. PILOT BATCH

- Taking into consideration drug-excipients compatibility study results, galenical development trials of extended release matrix tablets metoprolol tartrate employing wet granulation and compression technique, lab. pilot batch size was 200 gms.

7.B.6.1. Materials

- Drug: Metoprolol Tartrate (AstraZeneca)
- Polymer: HPMC K4M and HPMC K100M (Dow)
- Diluent: Lactose Monohydrate (Loba Chemicals)
- Lubricant: Magnesium Stearate (Loba Chemicals)
- Binding Agent: 90% V/V Alcohol (Ranbaxy)

7.B.6.2. Working batch Formula: The batch working formula is given below.

Table 7.4. Working batch formula for Pilot batch D.

Material	Category	Quantity
Metoprolol Tartrate	Active Drug	40 gms + 4gms (ove ge)
Hydroxypropyl methylcellulose (HPMC K4M)	Control Release Polymer	60 gms
Hydroxypropyl methylcellulose (HPMC K100M)	Control Release Polymer	40 gms
Lactose Monohydrate	Diluent	58 gms
Magnesium Stearate	Lubricant	02 gms
Alcohol (90% v/v)	Binding Agent	Quantity sufficient

7.B.6.3. Method

Wet granulation of metoprolol tartrate along with hydrophilic polymer, diluent and lubricant (half the quantity) was carried out in Kenwood Planetary mixer. The granules were dried at 60^{o}C, lubricated (adding remaining half the quantity) and compressed.

- **Shifting:** Metoprolol tartrate and the excipients were sifted through sieve # 60.
- **Dry Mixing:** Metoprolol tartrate, lactose and polymers were mixed for 10 minutes in Kenwood mixer at 30 rpm.
- **Sample analysis (for mixing):** Sample were scooped from different places and analyzed spectroscopically for uniform distribution of drug in the powder blend.
- Granulation: The powder blend was granulated using 90 % V/V alcohol.
- **Drying:** The wet granules were dried in tray direr at 60 ^{o}C (± 2) for 3-5 hours till loss of drying (LOD) of the granules was less than 5 % as determined by Karl Fisher Automatic Titration equipment.
- **Milling and Shifting:** The dried granules were sifted through sieve #18 and above mesh granules were milled in kitchen mixer. The milled granules were passed through sieve # 18 and mixed and sifted. LOD of granules was determined as mentioned earlier.

- **Lubrication:** The dried granules were blended with lubricantes in Kenwood mixer for 5.0 minutes at 20 rpm. Granule characteristic such as LOD, Particle Size Distribution, Density (tapped and untapped), Angle of Repose, Carr's Index and Hausner Ratio were determined.
- **Compression:** The lubricated granules are compressed on 16 station D-tooling single rotatory machine (Cadmach) using singe set of punch and die with the weight adjusted to 250 mg.

7.B.6.4. Process Optimization

- Effect of Particle Size: First trial batch was carried using supplier's material passed through sieve # 60. Remaining batches were carried out post-micronization of the drug (# 120).
- Effect of Moisture: The moisture content was varied between 0.5 – 5.0 % w/w and its effect on compressibility of Metoprolol tartrate granules was evaluated.

7.B.7. PILOT BATCH EVALUATION

7.B.7.1. Tests As Described Earlier

The evaluating tests for the pilot batch D were same as earlier batches with supplemented with few more tests described in the following sections based in line with the requirements of NDA and SUPAC; however only *in vivo* tests were not performed. This batch product was also compared with the Reference Listed Drug (RLD) in an attempt to compare the developed product with the innovators product.

7.B.7.2. Reference Listed Drug: For Metoprolol ER Dosage Form

The label details of the RLD of the strength available in the Indian market are given below.

R_x Metoprolol Succinate Extended Release Tablets USP

Seloken® XL 50 mg

Each extended release film coated tablet contains Metoprolol Succinate USP 47.5 mg equivalent to Metoprolol Tartrate 50 mg. Color Titanium Dioxide

Dosage: As directed by the Physician.

Direction for use: The tablets or the divided halves of the tablets should be taken 'th water, do not crush or chew the tablets.

Precaution: Schedule H drug.
Warning: To be sold by retail on the prescription of a Registered Medical Practitioner only.

Storage: Do not store above 30 ^{O}C. Protect from light.

Manufacturing License Number: 30-141-23
Batch Number: SXF DO11
Manufacturing date: 07/2003 Expiry date: 06/2006
Retail Price: Not to exceed Rs. 59.60 for 7 tablets. Local Taxes Extra.
Mfg. by: AstraZeneca Pharma India Ltd, 12th Mile, Bellary Rd, Bangalore – 560 063.

7.B.8. EXPOSURE STUDIES AND SHORT TERM STABILITY STUDY FOR EVALUATION OF LABORATORY SCALE DEVELOPED FORMULATION

7.B.8.1. Thermal Exposure of granules

MT lubricated granules (10 gms) were packed in an HDPE container and subjected to temperature of 60 ± 2 ^{O}C in an oven for 7 day. The granules post exposure, were compressed and the effect on tablet characteristics were compared with tablet characteristics observed for unexposed granules. The *in vitro* dissolution data as % cumulative release versus time is plotted.

7.B.8.2. Exposure study of granules and tablets at 40 ^{O}C/ 75% RH and 8-10 ^{O}C/ 60% RH

MT granules (10 gms) and 20 tablets were directly exposed in an open petri-plate at 40 ^{O}C/ 75% RH and 8-10 ^{O}C/ 60% RH for 7 days to get a preview of its stability.

7.B.8.3. Accelerated Stability Study

Based on the results of initial exposure studies, the tablets were blister packed in clear PVC /PVDC 40 gsm (PVC/ PVDC 40 GSM – Bilcare) with a lidding membrane of Aluminium, 0.03 mm; using Pharmpack 240 Blister Packing Machine. In-process testing such as leak test under vacuum, physical observation of blister were

performed to ensure packing. The blisters were subjected to stability studies under different conditions (as per ICH Guidelines) described in Ch. 6, Section 6.12.2.

Table 7.5. Conditions for short term stability evaluation of MT ER tablets (batch D).

Incubation Conditions	Withdrawal Period (in months)	Number of Packs
30 ^{O}C/ 65% RH	1, 2 and 6	10 blisters /condition
40 ^{O}C/ 75% RH	1, 2 and 6	10 blisters /condition
8-10 ^{O}C/ 60% RH	1, 2 and 6	10 blisters /condition
Photo Stability Chamber	1, 3	10 blisters /condition

The tablets after the specified incubation periods were withdrawn and evaluated to ascertain their physical and chemical stability employing standard reported procedures.

Table 7.6. Stability evaluating parameters for Metoprolol Tartrate ER tablets (Batch D).

Physical Parameters	**Chemical Parameters**
Appearance of Tablet and the Pack	Assay
Thickness of Tablet	Dissolution
Average Weight of the Tablet	
Hardness	
Loss on Drying	
Friability	

7.B.9. DIMENSIONAL SWELLING STUDIES (Under Static Conditions) [21]

The tablet was glued to a glass plate and kept immersed in pH 6.8 phosphate buffer solution at room temperature. At periodic time intervals (0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, and 10 hours), the change in the radial and axial dimensions of the swelling matrix were measured using Vernier Calipers, with minimal damages caused to the gelled matrix. The tablet was replaced again immersed in the medium. The experiment was repeated 6 times and the average of 6 readings was taken. The normalized tablet dimensions estimated using the following equation:

Normalized radial dimension = $R_{(t)}/R_{(0)}$

and ***Normalized axial dimension*** = $A_{(t)}/A_{(0)}$

where $R_{(0)}$ and $A_{(0)}$ are the dimensions at time = 0; $R_{(t)}$ and $A_{(t)}$ are the dimensions at the time = t.

7.B.10. MATHEMATICAL MODELS FOR RELEASE KINETICS

7.B.10.1. Zero Order Model

Mathematically, the zero order release rate is represented by the following equation

$$dc/dt = k_0$$

where c = concentration of drug release, t = time of release and k_0 = Zero order release constant. The values of the % drug release and time were fitted in the above equation to determine the suitability of this model by plotting a graph of % cumulative drug release versus time.

7.B.10.2. First order model

Mathematically, the first order rate is represented by the following equation

$$\log W = \frac{kt}{2.303} + \log W_0$$

where W = amount of the drug left in the matrix, W_0 = initial amount of the drug in the matrix, k = first order release constant time^{-1} and t= time. The values of the % drug release and time were fitted in the above equation to determine the suitability of this model by plotting a graph of log of cumulative % drug release versus time.

7.B.10.3. Higuchi Model

Higuchi model to study release of drug is based on following equation

$$F_t = Q = [D\,(2C-C_s).\,C_s t]^{1/2}$$

where $F_t = Q$ = amount of drug release in time t; C = initial drug concentration; C_s = drug solubility in the matrix media; and D = diffusion coefficient.

The values of % drug release and time were fitted into simplified Higuchi equation, which is as follows

$$Q = kt^{1/2}$$

where k = Higuchi dissolution constant. A graph of amount of drug release in time t versus square root of time was plotted to describe the model.

7.B.10.4. Hixon-Crowell Model

Hixon Crowell model is described by the following equation

$$W_0^{1/3} - W_t^{1/3} = K_s\, t$$

where W_0 = initial amount of drug in the dosage form, W_t = drug remaining in dosage form at time t and K_s = constant incorporating surface – volume relation. The model

is described by plotting the graph of cube root of fraction drug unreleased versus time.

7.B.10.5. Korsmeyer - Peppas Model

Korsmeyer – Peppas model is described by the following equation

$$M_t / M_\infty = a.\, t^n$$

Where M_t / M_∞ = fraction drug released and n = release exponent indicative of drug release mechanism. The model is described by plotting the graph of log fraction drug release versus log time.

7.B.10.6. Similarity Factor

In recent years, FDA has placed emphasis of a dissolution profile comparison in the area of post-approval changes and biowaivers. Under appropriate test conditions, a dissolution profile can characterize the product more precisely than a single point dissolution test. A dissolution profile comparison between pre-change and post-change products for SUPAC related changes, or with different strengths, helps assure similarly in product performance and signals bioinequivalence. The similarity factor adopted by US FDA was calculated using the formula

$$f_2 = 50.\log\left\{1+\left(\frac{1}{n}\right).\left[\sum_{t=1}^{n}\left(R_t - T_t\right)\right]^{-\frac{1}{2}}\right\}.100$$

where R_t = % drug release of reference product at each time point t; T_t = % drug release of test product at each time point t and n = sampling number.

7.B.10.7. Difference Factor

The difference factor adopted by US FDA was calculated using the formula

$$f_1 = \left\{\frac{\left[\sum_{t=1}^{n}\left|R_t - T_t\right|\right]}{\left[\sum_{t=1}^{n} R_t\right]}\right\}.100$$

where R_t= % drug release of reference product at each time point t; T_t = % drug release of test product at each time point t and n = sampling number.

The factor f_1 is proportional to the average difference between the two profiles; where as factor of f_2 is inversely proportional to the average squared difference between the two profiles, with emphasis on the larger difference among all the time points. The factor f_2 measures the closeness between the two profiles.

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Chapter 8

Results & Discussion......

8.1. PREFORMULATION STUDIES

8.1.1. Physicochemical Characteristics of Metorpolol Tartrate

The tests reports for MT along with the literature values are given in Table 8.1.

Table 8.1. Preformulation data for Metoprolol Tartrate.

Parameters	Observed Values	Reported Values
UV- spectral Absorption (λ_{max})	224 nm & 275 nm	275 nm
Melting Point	123 ^{O}C	121 –124 ^{O}C
pH	6.6	6.0 - 7.0
pKa	-	8.9 - 9.5 (± 0.2) at 8 x 10^{-4} M in water at 25 ^{O}C
Moisture Content (Karl Fisher Titration)	0.61	> 0.5 %
Density A. Bulk (gm/mL) B. Tap (gm/mL)	0.56 0.67	- -
Bulkiness (cm^3/gm)	1.782	-
Flowability (Angle of Repose)	45^{O}23$'$	-
Carr's Index	16.41	-
Hausner Ratio	1.20	-

8.1.2. Particle Size Distribution in Polymer HPMC

The particle size distribution determined by sieve analysis is given in Table 8.2 and the value plotted (fig. 8.1 and 8.2). The product literature attachment for the free gift sample of polymer HPMC by Colorcon Asia specifies that minimum of 90.0% of polymer pass through sieve no. 40 US standard sieve, while our studies show that both the grades of polymer passed through sieve # 45.

Table 8.2. Particle size distribution in HPMC K4M and HPMC K100M.

Sieve Number	Nominal # Size (μm)	% Weight Distribution		Cumulative % Under Size	
		HPMC K4M	HPMC K100M	HPMC K4M	HPMC K100M
# 45	355	-	2.35	Passed	100.00
# 60	250	2.23	2.78	100.00	97.65
# 80	180	7.27	3.70	97.77	94.87
# 100	150	9.94	5.82	90.50	91.16
# 120	125	10.81	6.04	80.56	85.34
# 120 passed	> 125	69.75	79.30	69.75	79.30
	Total =	~100.00	~100.00		

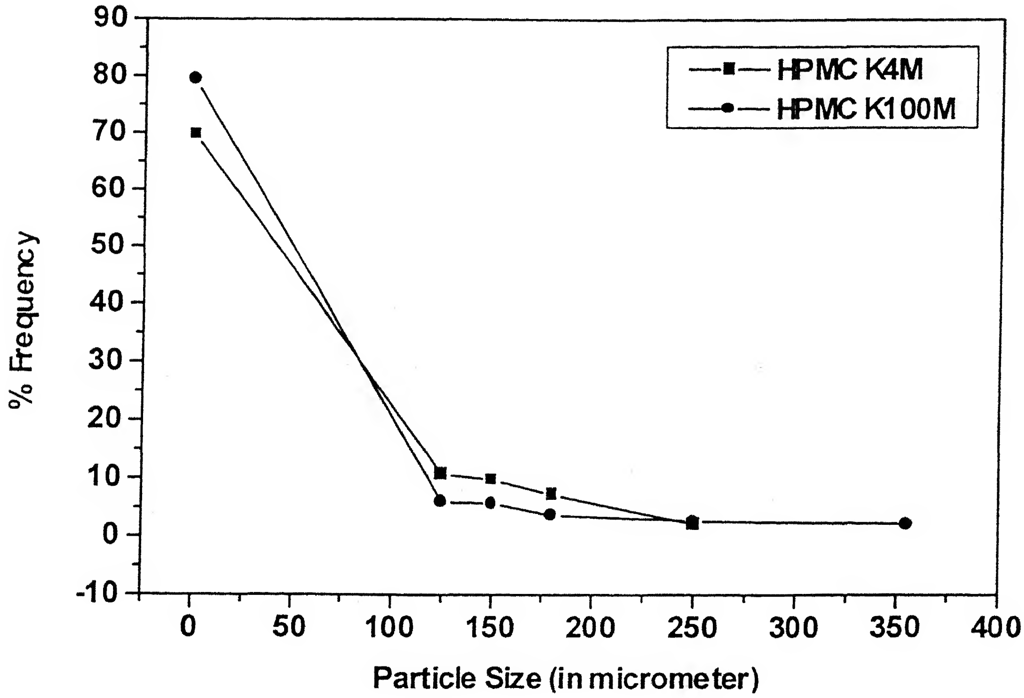


Fig.8.1. Percent frequency particle size distribution in HPMC K4M and K100M.

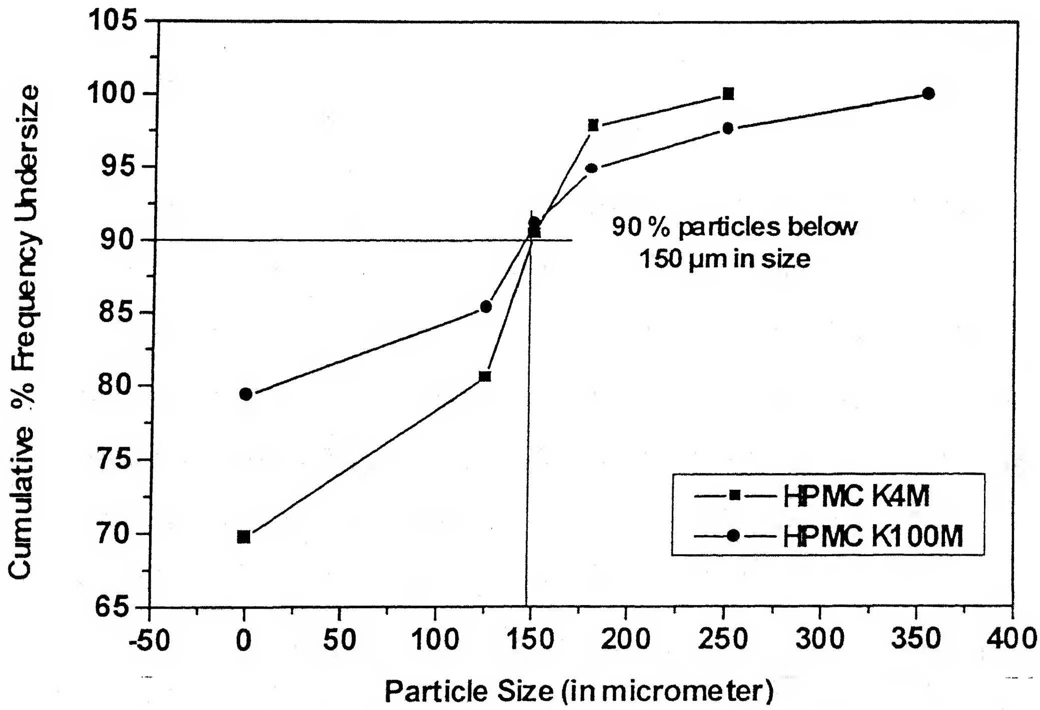


Fig. 8.2. Percent cumulative frequency undersize in HPMC K4M and K100M.

Fig. 8.1 exhibits that ~70 % of the low molecular weight polymer (HPMC K4M) passed through sieve # 120 while ~79% higher molecular weight polymer (HPMC K100M) passed through same sieve. This is indicative that the higher molecular weight comprised of finer particles. As the values are further analyzed, it's noted that there is uniform and gradual decrease in the quantity of particles retained on larger sieve size in both the grades of polymer, however the ratio is more in case of K4M. All the K4M powder passed through sieve # 60 while 2.35% of HPMC K100M was retained. Fig. 8.2 depicts that 90% of the particles of HPMC K4M and HPMC K100M are below # 150 micrometer in size and it's this size particles which would be influencing the release profiles of the developed tablet matrix system.

8.1.3. Drug-Excipient Compatibility Studies

8.1.3.A. Fourier Transform Infra Red Spectroscopy

Infra Red (IR) spectra are being used in confirming identities by comparing the spectra of two samples to each other to determine whether the samples have the same composition[1].

The FTIR spectra for pure drug MT, controlled release low molecular weight polymer HPMC K4M and high molecular weight polymer HPMC K100M, diluent lactose monohydrate and lubricant magnesium stearate with its transmittance peak values are given in Fig. 8.3 to 8.7 respectively. The spectra for the drug and polymer mixture with low and high-density molecular weight polymer are shown in Fig. 8.8 and 8.9 respectively; and with lactose and magnesium stearate in Fig. 8.10 and 8.11 along with its peak absorption values. An overlay of FTIR spectra of pure drug MT (curve A), pure polymer HPMC K4M (curve B); and MT and HPMC K4M (curve C) and are shown in Fig. 8.12. The characteristic peaks of the drug (curve A) and that

in the mixture of drug and polymer (curve C) are found overlaying. This is indicative absence of interactions that could be leading to chemical changes in the drug. Therefore, HPMC can be said to be compatible with the drug. Similar results were obtained for high-molecular weight polymer (Fig. 8.13), lactose (Fig. 8.14) and magnesium stearate (Fig. 8.15).

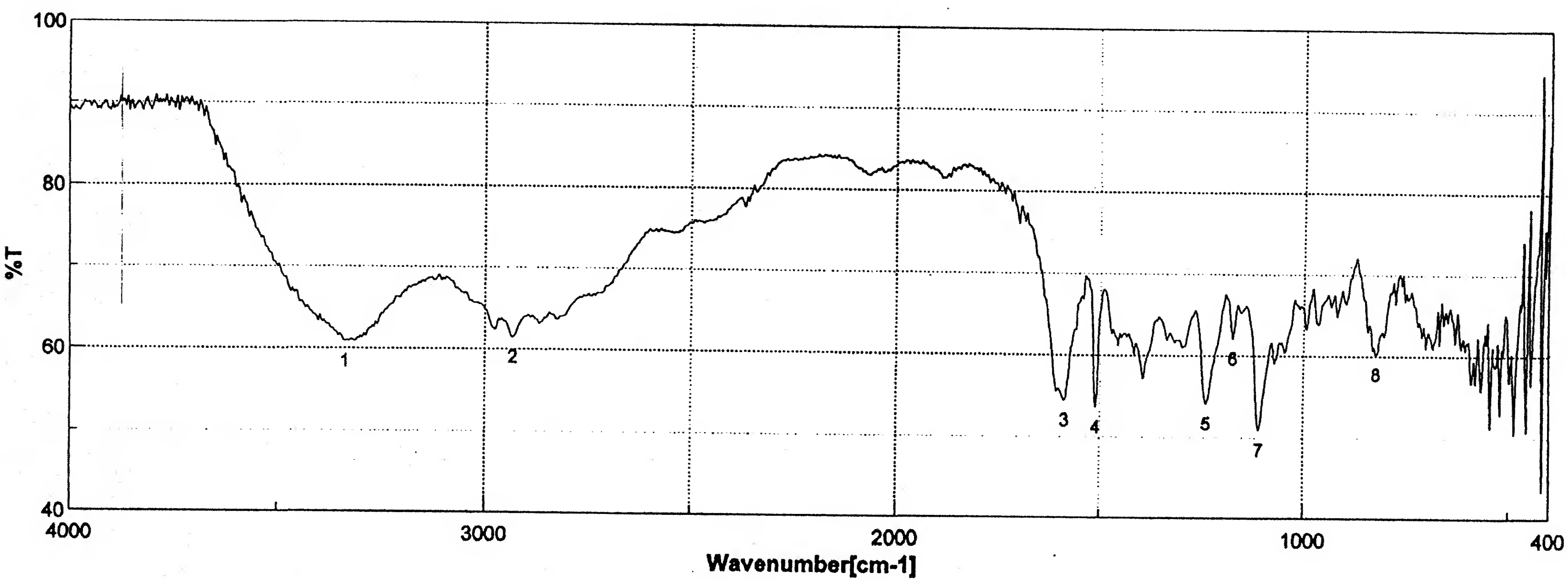
8.1.3.B. Chromatography

The chromatograms developed as per the modified USP 27 method for the pure drug and mixtures of drug and polymer and excipients is given in Ch. 7, Section 7. B.1.7.ii.

8.1.3.B.i. Development of Spots

After developing the chromatogram and spraying with the indicator, four distinguished spots were observed almost at the distance movement of solvent front (15 cm) from the four different spots, spotted with as pure drug MT (spot A); mixtures of MT and polymer HPMC K4M (spot B), MT and diluent lactose monohydrate (spot C), MT and lubricant magnesium stearate (spot D) in the first chromatorgram (fig. 8.16). Similar results were obtained in other chromatogram developed with high-density polymer and other excipients viz., MT (spot E); mixtures of MT and polymer HPMC K100M (spot F), MT and lactose monohydrate (spot G), MT and lubricant magnesium stearate (spot H) (fig. 8.17) with the solvent and solute front moved to a distance of 14.8 cm.

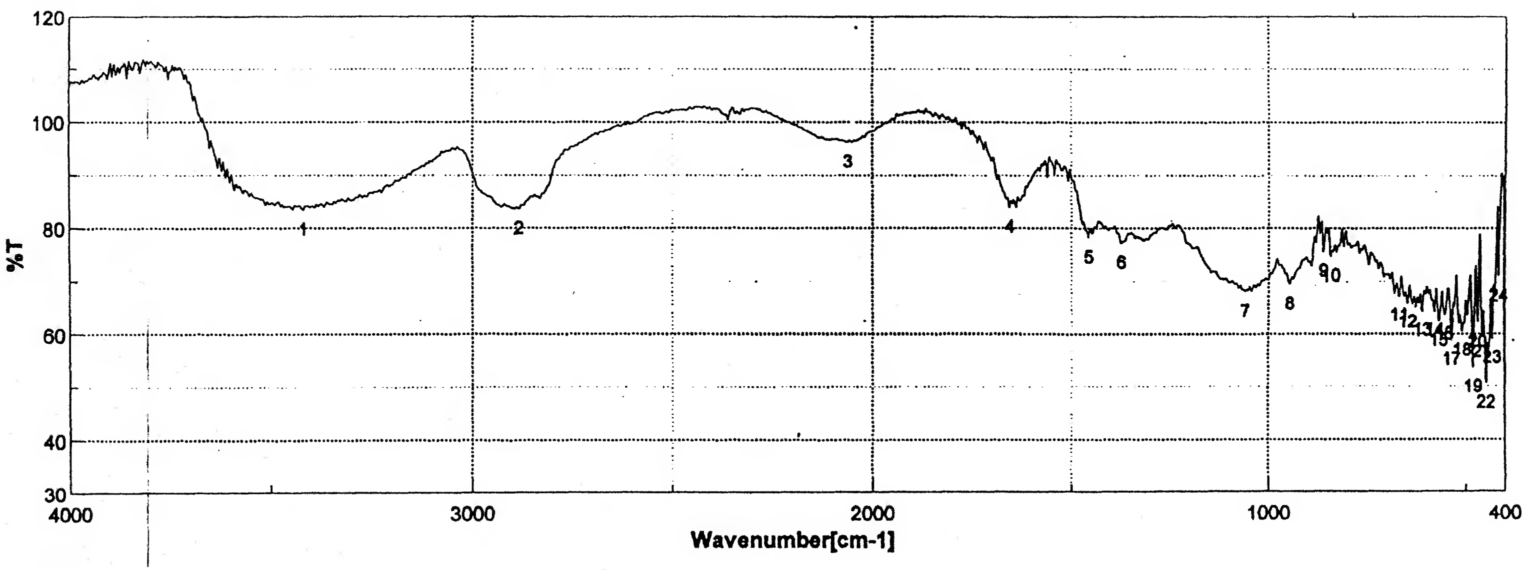
Relative comparison of spots A, B, C and D indicate that the area of spot B (mixture of MT and polymer HPMC K4M) is larger than others, pointing to its greater diffusivity however other spots were more condense. Similar results were found with in the second chromatogram (spot E) with HPMC K100M high-density polymer forming a bigger developed spot size than the spot B. These results indicate that the polymer HPMC helped to carry the drug as it diffused under the influence of movement of solvent front once it traveled the characteristic R_f value.



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	Auto (64)	Scanning Speed	Auto (2 mm/sec)
Date/Time	1/18/05 3:59PM	Update	2/5/05 0:24PM
Operator	BM DINESH		
File Name	Metoprolol Tartrate		
Sample Name	drug mt		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3340.1	60.9003	2	2934.16	61.4636	3	1588.09	54.4523	4	1511.92	53.6335	5	1243.86	54.1174
6	1179.26	62.0342	7	1111.76	50.9279	8	825.384	60.1771						

Fig. 8.3. FTIR spectra for pure drug metoprolol tartrate along with absorption peak values.

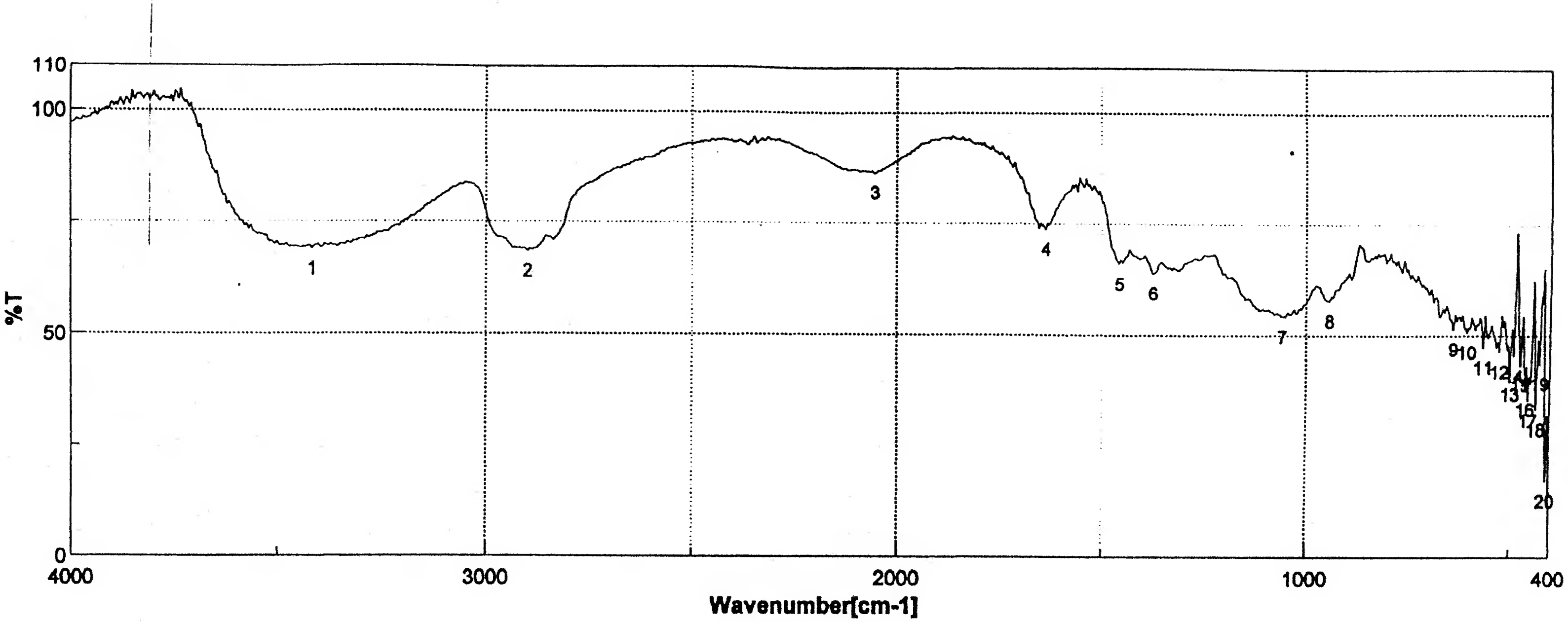


Accumulation	16	
Zero Filling	ON	
Gain	Auto (64)	
Date/Time	1/18/05 4:23PM	
Operator	BM DINESH	
File Name	Hpmc k4m	
Sample Name	drug mt	
Comment		

Resolution	4 cm-1
Apodization	Cosine
Scanning Speed	Auto (2 mm/sec)
Update	2/5/05 0:27PM

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3422.06	83.4106	2	2887.88	83.5804	3	2063.46	96.1928	4	1653.66	83.9303	5	1457.92	78.3295
6	1376.93	77.2789	7	1060.66	68.0875	8	947.841	69.5278	9	863.953	75.6629	10	845.633	74.7771
11	671.106	67.3143	12	649.893	65.955	13	612.288	64.3449	14	580.469	64.3075	15	569.862	62.4128
16	555.398	63.669	17	536.114	58.7608	18	509.115	60.5243	19	481.153	53.542	20	469.582	62.1698
21	458.011	60.1379	22	447.404	50.5755	23	431.977	59.0723	24	415.585	71.0516			

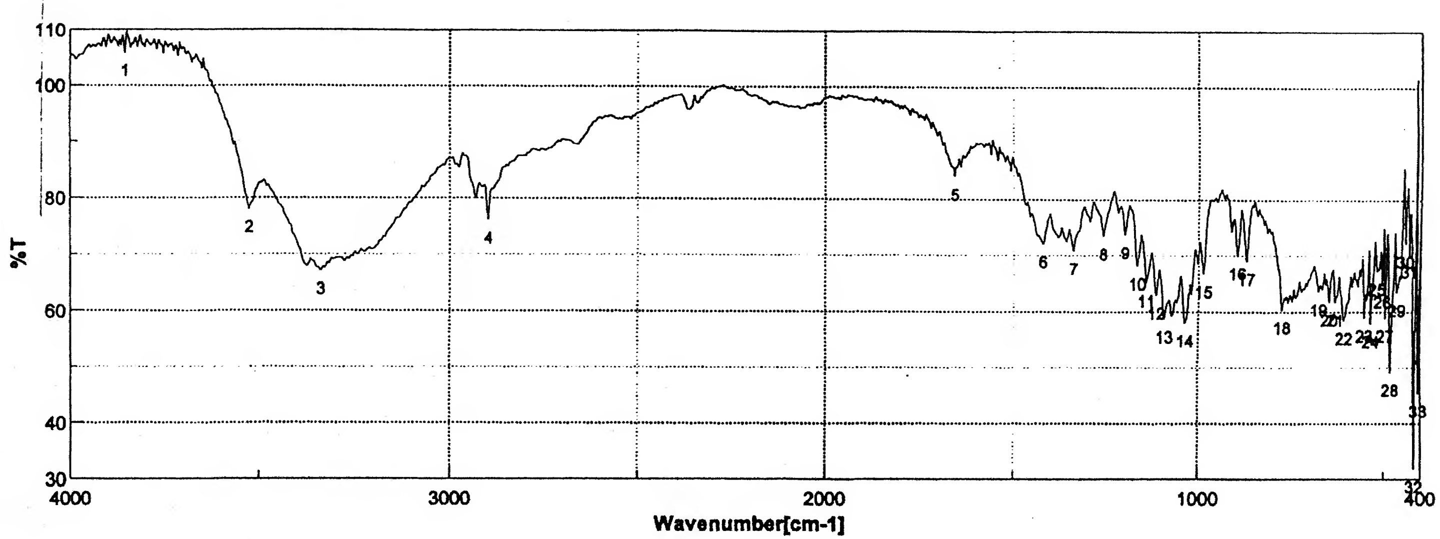
Fig. 8.4 FTIR spectra for low molecular weight polymer HPMC K4M along with absorption peak values.



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	Auto (64)	Scanning Speed	Auto (2 mm/sec)
Date/Time	1/18/05 4:11PM	Update	2/5/05 0:28PM
Operator	BM DINESH		
File Name	HPMC K100M		
Sample Name	drug mt		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3418.21	68.8324	2	2901.38	68.2406	3	2054.78	86.166	4	1638.23	73.5344	5	1457.92	65.814
6	1375	63.6723	7	1060.66	54.1224	8	944.949	57.5904	9	640.251	51.3304	10	607.467	50.6142
11	566.969	47.2745	12	526.471	46.3455	13	500.437	41.2653	14	490.795	45.4153	15	474.403	43.2905
16	461.868	37.8516	17	454.154	35.4168	18	434.869	33.3963	19	426.191	43.5629	20	409.799	17.3734

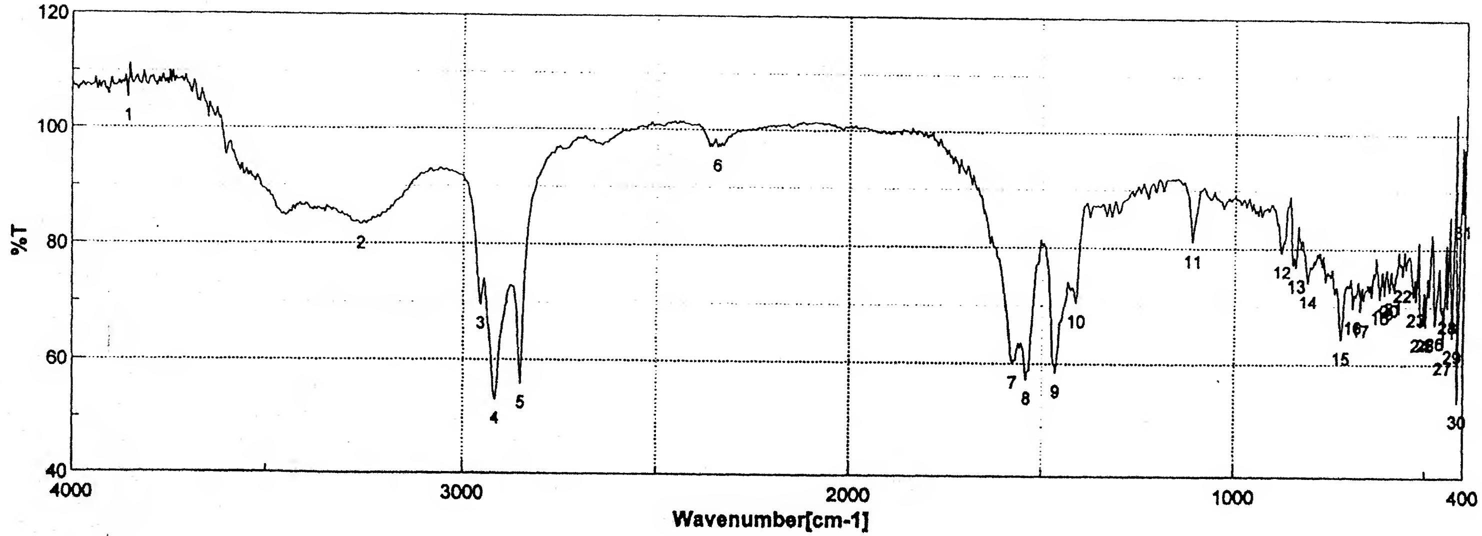
Fig. 8.5. FTIR spectra for high molecular weight polymer HPMC K100M along with absorption peak values.



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	Auto (64)	Scanning Speed	Auto (2 mm/sec)
Date/Time	1/18/05 4:18PM	Update	2/5/05 0:29PM
Operator	BM DINESH		
File Name	Lactose		
Sample Name	drug mt		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3854.04	105.742	2	3526.2	77.9678	3	3339.14	67.0187	4	2899.45	75.9865	5	1654.62	84.0406
6	1422.24	72.0313	7	1340.28	70.7396	8	1260.25	73.3707	9	1201.43	73.6576	10	1167.69	68.086
11	1142.62	65.0928	12	1115.62	62.9306	13	1093.44	58.6875	14	1037.52	58.0039	15	988.339	66.7298
16	899.63	69.9275	17	875.524	68.9461	18	779.101	60.3104	19	679.785	63.5417	20	649.893	61.7393
21	633.501	61.6986	22	608.431	58.4042	23	552.506	58.8311	24	535.15	57.8726	25	518.758	67.2086
26	504.294	64.9901	27	495.616	58.8412	28	481.153	49.1853	29	463.796	63.456	30	441.619	72.0548
31	431.012	70.2449	32	417.513	31.8497	33	405.942	45.3655						

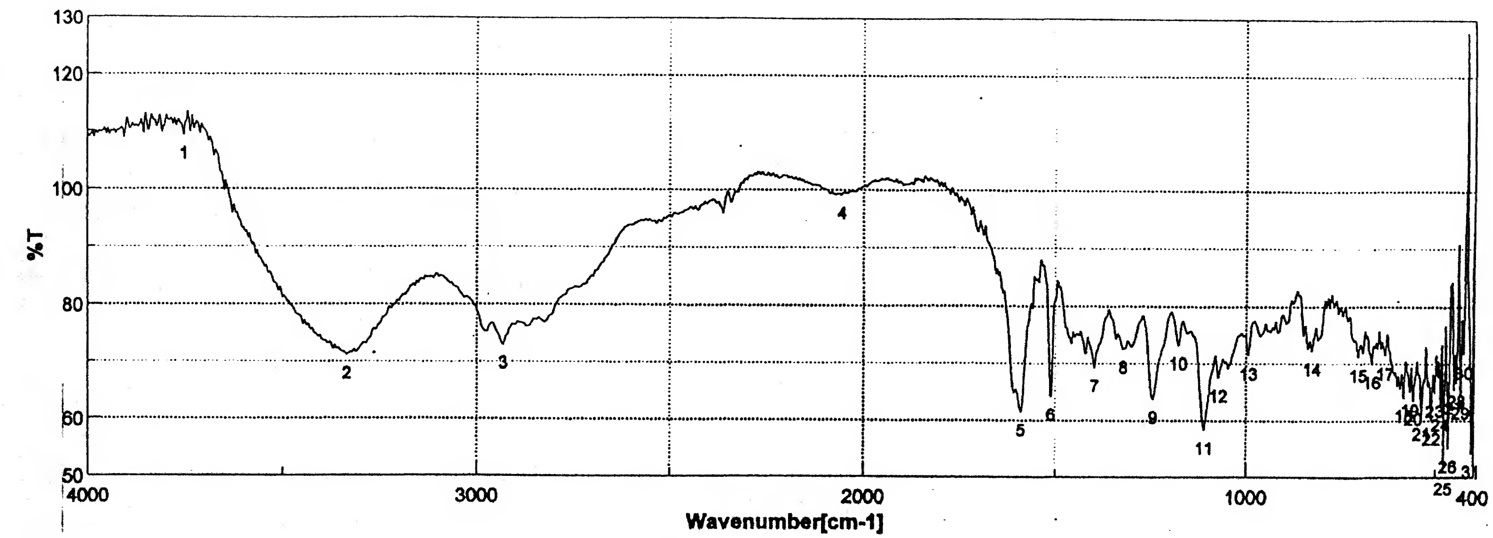
Fig. 8.6. FTIR spectra for diluent lactose monohydrate along with absorption peak values.



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	Auto (64)	Scanning Speed	Auto (2 mm/sec)
Date/Time	1/18/05 4:33PM	Update	2/5/05 0:29PM
Operator	BM DINESH		
File Name	Magnesium Stearate		
Sample Name	drug mt		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3854.04	105.177	2	3259.11	83.2558	3	2955.38	69.481	4	2916.81	52.9889	5	2849.31	55.7599
6	2345.02	97.0499	7	1577.49	59.8848	8	1541.81	57.1653	9	1465.63	58.3563	10	1413.57	70.5078
11	1113.69	80,9935	12	880.345	79.2159	13	841.776	76.7928	14	810.92	74.0265	15	721.247	64.292
16	690.391	69.6479	17	670.142	69.1723	18	619.038	71.4391	19	607.467	72.1513	20	594.932	72.6123
21	583.361	72.9991	22	561.184	75.3133	23	525.507	71.0389	24	513.936	66.6499	25	500.437	66.629
26	475.367	66.9223	27	453.19	62.7507	28	443.547	69.8108	29	430.048	64.6962	30	415.585	53.3852
31	406.907	86.2892												

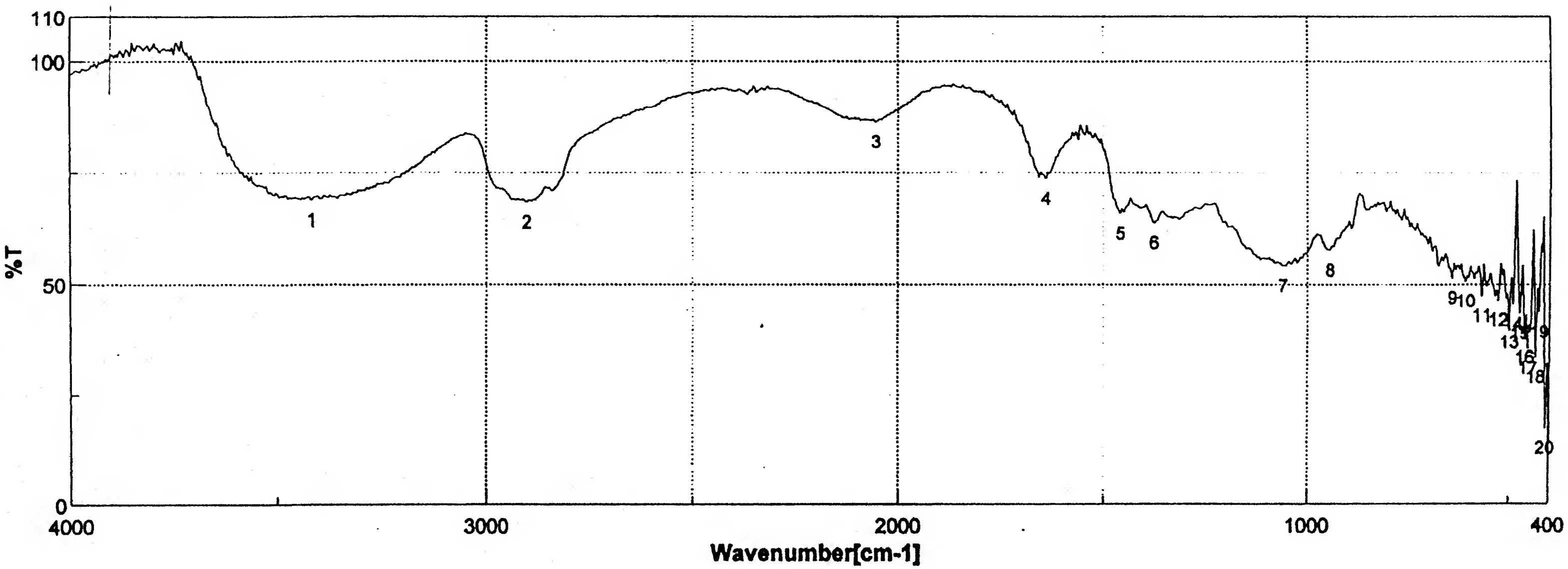
Fig. 8.7. FTIR spectra for lubricant magnesium stearate along with absorption peak values.



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	Auto (64)	Scanning Speed	Auto (2 mm/sec)
Date/Time	1/18/05 4:27PM	Update	2/5/05 0:30PM
Operator	BM DINESH		
File Name	Drug, Drug + K4M, K4M		
Sample Name	drug mt		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3751.83	109.211	2	3337.21	71.0785	3	2933.2	72.9389	4	2057.67	99.1085	5	1590.02	61.4726
6	1511.92	64.1784	7	1397.17	69.3001	8	1321	72.564	9	1243.86	63.6733	10	1178.29	73.1913
11	1110.8	58.3663	12	1073.19	67.5088	13	995.089	71.4139	14	829.241	72.1911	15	705.819	71.1243
16	669.178	69.8996	17	633.501	71.4312	18	584.325	64.0641	19	567.934	65.0502	20	559.255	63.4611
21	537.078	60.923	22	511.044	60.0827	23	502.366	64.8749	24	486.938	62.489	25	478.26	51.2904
26	466.689	55.1256	27	451.261	65.4306	28	445.476	66.6708	29	434.869	64.6015	30	426.191	71.5832
31	405.942	54.2016												

Fig. 8.8. FTIR spectra for mixture of metoprolol tartrate and HPMC K4M along with absorption peak values.

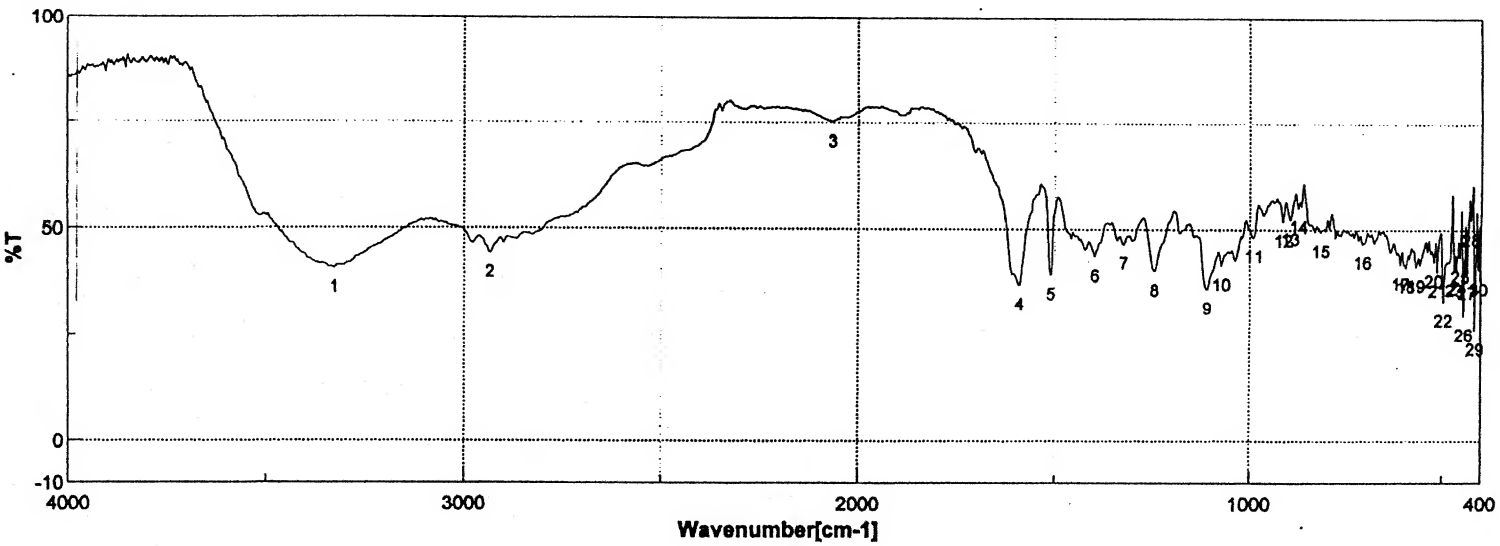


Accumulation	16
Zero Filling	ON
Gain	Auto (64)
Date/Time	1/18/05 4:11PM
Operator	BM DINESH
File Name	Drug, Drug + K100M, K100M
Sample Name	drug mt
Comment	

Resolution	4 cm-1
Apodization	Cosine
Scanning Speed	Auto (2 mm/sec)
Update	2/5/05 0:30PM

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3418.21	68.8324	2	2901.38	68.2406	3	2054.78	86.166	4	1638.23	73.5344	5	1457.92	65.814
6	1375	63.6723	7	1060.66	54.1224	8	944.949	57.5904	9	640.251	51.3304	10	607.467	50.6142
11	566.969	47.2745	12	526.471	46.3455	13	500.437	41.2653	14	490.795	45.4153	15	474.403	43.2905
16	461.868	37.8516	17	454.154	35.4168	18	434.869	33.3963	19	426.191	43.5629	20	409.799	17.3734

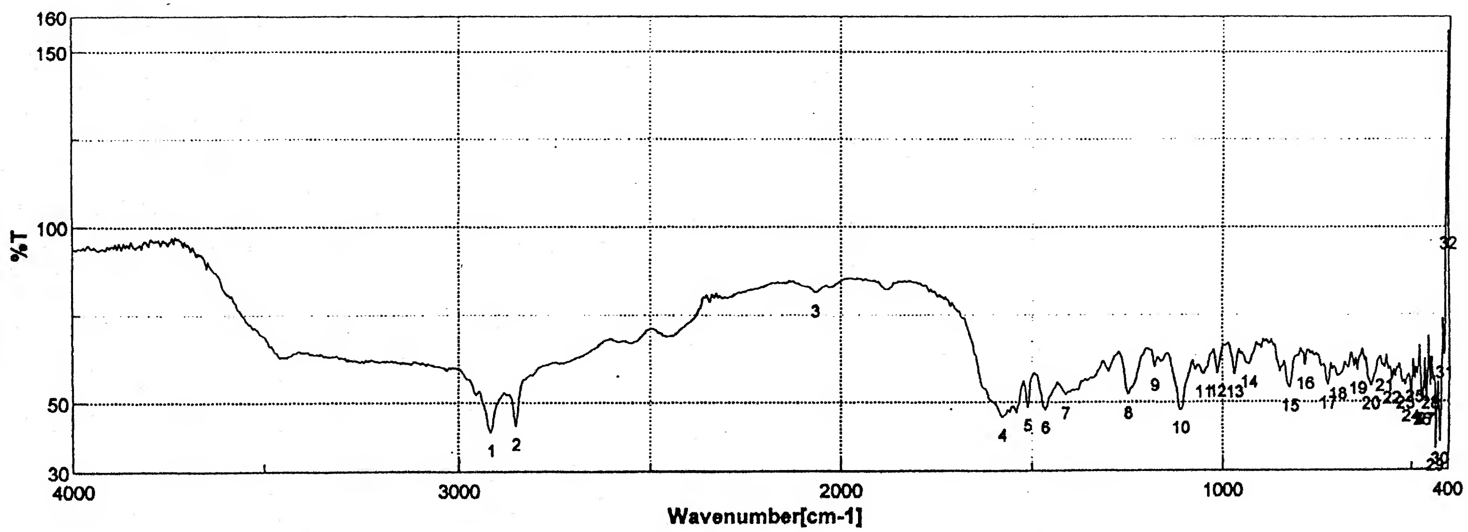
Fig. 8.9. FTIR spectra for mixture of metoprolol Tartrate and HPMC K100M along with absorption peak values.



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	Auto (64)	Scanning Speed	Auto (2 mm/sec)
Date/Time	1/18/05 4:50PM	Update	2/5/05 0:31PM
Operator	BM DINESH		
File Name	Drug, Drug+Lactose, Lactose		
Sample Name	drug mt		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3327.57	40.6031	2	2935.13	44.203	3	2066.35	75.1039	4	1590.02	36.7511	5	1511.92	39.1885
6	1396.21	43.4951	7	1321.96	46.4814	8	1242.9	40.0782	9	1109.83	35.7914	10	1073.19	41.4154
11	991.232	48.0803	12	916.022	51.8392	13	897.701	52.2022	14	876.488	55.0559	15	819.598	49.3502
16	708.712	46.6158	17	609.396	41.6092	18	594.932	40.9907	19	568.898	41.1061	20	522.615	42.2827
21	512.972	39.9853	22	497.544	32.8148	23	469.582	40.1739	24	462.832	40.4678	25	455.118	43.3416
26	445.476	29.4091	27	436.798	39.4766	28	427.155	52.0694	29	416.549	25.9876	30	406.907	40.3635

Fig. 8.10. FTIR spectra for mixture of metoprolol tartrate and lactose monohydrate along with absorption peak values.



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	Auto (64)	Scanning Speed	Auto (2 mm/sec)
Date/Time	1/18/05 4:40PM	Update	2/5/05 0:31PM
Operator	BM DINESH		
File Name	Drug, Drug+Mag.stearate, Mag.stearate		
Sample Name	drug mt		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	2915.84	41.3633	2	2849.31	43.1931	3	2067.32	81.2123	4	1578.45	45.5642	5	1511.92	48.4352
6	1464.67	47.8135	7	1410.67	52.005	8	1248.68	52.0274	9	1179.26	59.98	10	1112.73	47.7098
11	1051.01	58.0018	12	1014.37	58.1688	13	967.126	57.9636	14	928.557	60.794	15	819.598	54.0742
16	779.101	60.3661	17	718.354	54.8204	18	693.284	57.334	19	641.215	58.9138	20	606.503	54.5663
21	571.79	59.6992	22	552.506	56.0854	23	517.793	54.6908	24	503.33	50.8592	25	493.688	56.4736
26	472.474	49.9657	27	461.868	50.0795	28	451.261	54.596	29	435.834	36.5508	30	423.298	38.431
31	413.656	63.303	32	401.121	100.206									

Fig. 8.11. FTIR spectra for mixture of metoprolol tartrate and magnesium stearte along with absorption peak values.

8.1.3.B.ii. R_f value

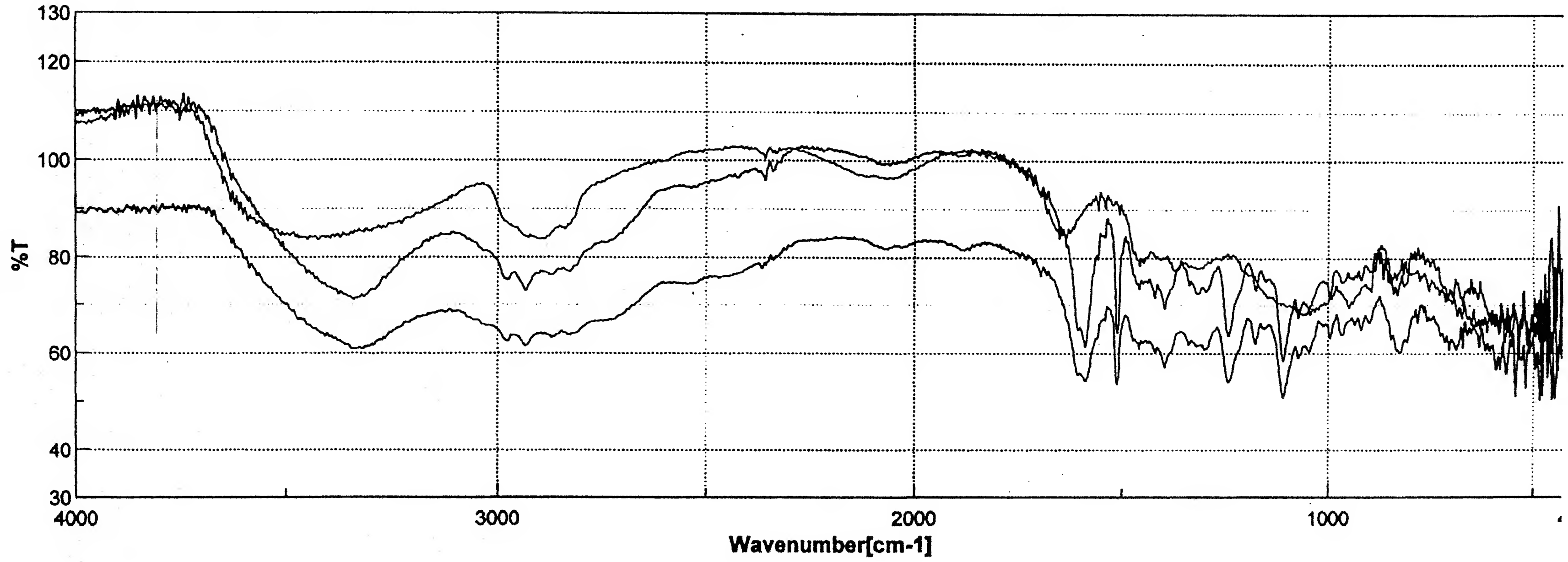
The R_f value for the drug and drug in the mixture was determined and tabulated in Tables 8.3 and 8.4 for low and high-density HPMC polymers. The unchanged R_f value for the pure drug and drug in the mixtures is indicative of absence of incompatibility between the drug, polymer and the xcipients chosen for the development of controlled drug delivery system.

Table 8.3. R_f values for the drug and drug in mixtures low density polymer (HPMC K 4M) and with excipients.

Test Solution	**Spot**	**Solute Front (in cm)**	**Solvent Front (in cm)**	**R_f Value**
Metoprolol Tartrate	A	15	15	1
Metoprolol Tartrate + HPMC K4M	B	15	15	1
Metoprolol Tartrate + Lactose monohydrate	C	15	15	1
Metoprolol Tartrate + Magnesium Stearate	D	15	15	1

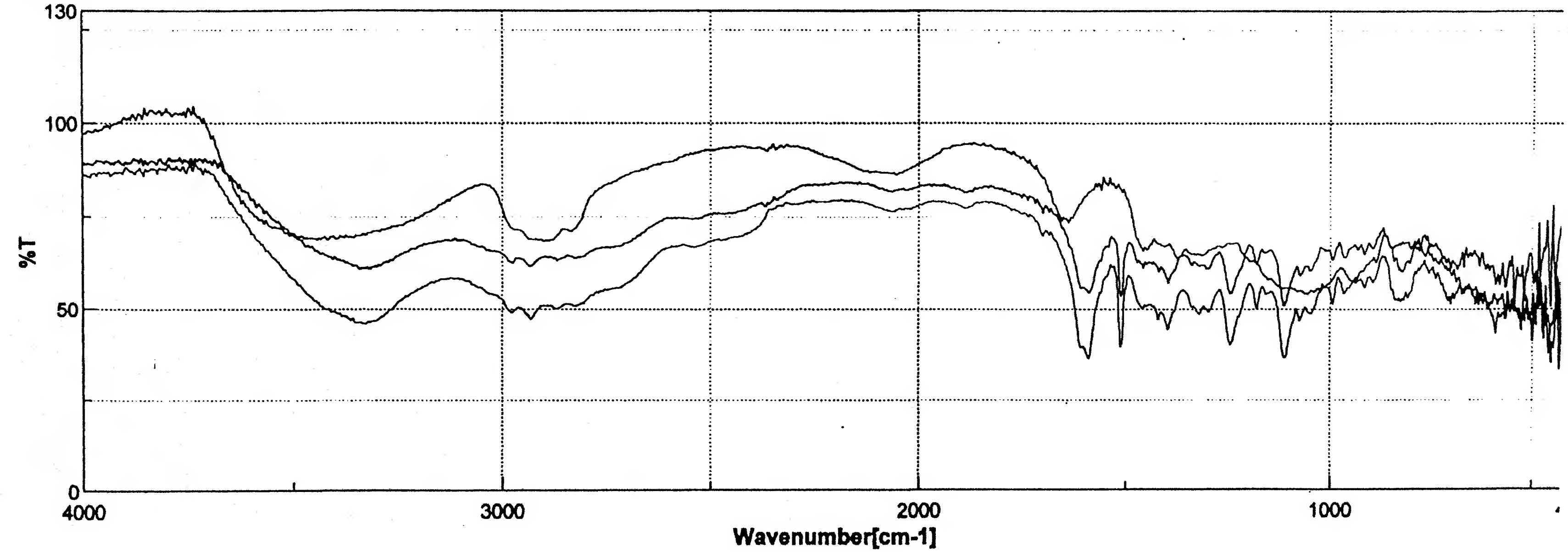
Table 8.4. R_f values for the drug and drug in mixtures low density polymer (HPMC K 100M) and with excipients.

Test Solution	**Spot**	**Solute Front (in cm)**	**Solvent Front (in cm)**	**R_f Value**
Metoprolol Tartrate	E	14.8	14.8	1
Metoprolol Tartrate + HPMC K100M	F	14.8	14.8	1
Metoprolol Tartrate + Lactose monohydrate	G	14.8	14.8	1
Metoprolol Tartrate + Magnesium Stearate	H	14.8	14.8	1



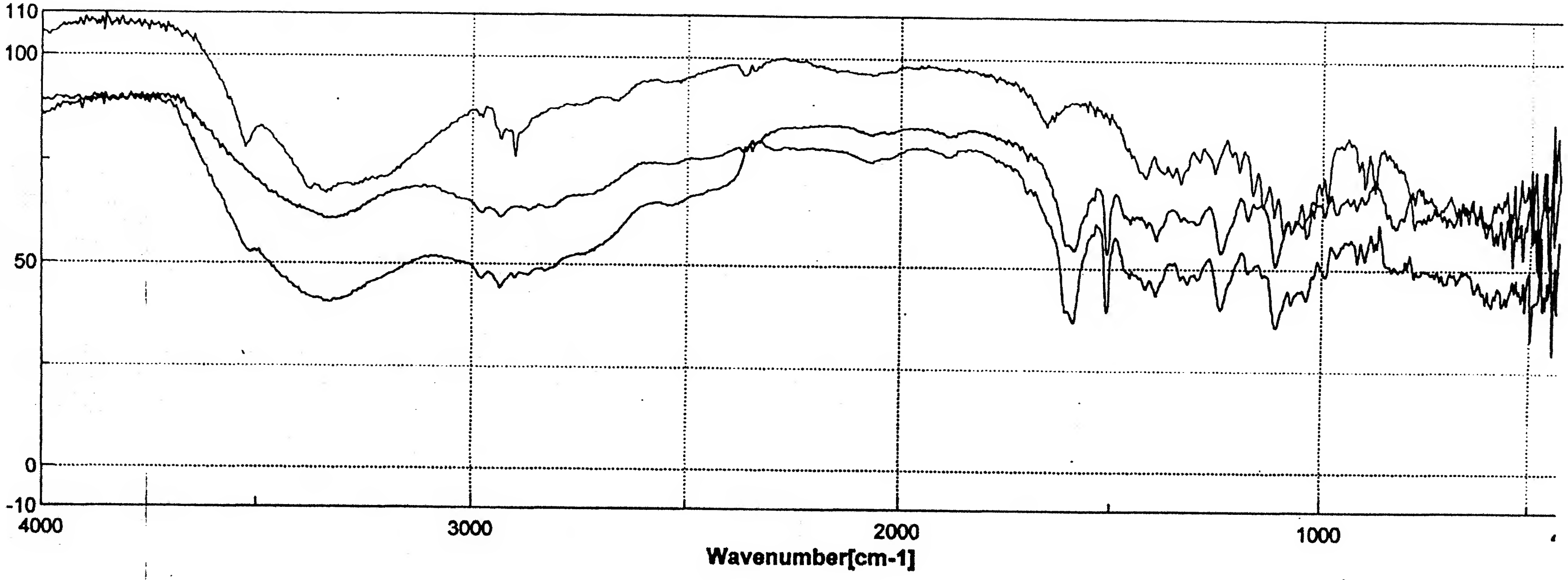
Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	Auto (64)	Scanning Speed	Auto (2 mm/sec)
Date/Time	1/18/05 3:59PM	Update	2/5/05 0:25PM
Operator	BM DINESH		
File Name	Metoprolol Tartrate		
Sample Name	drug mt		
Comment			

Fig. 8.12. FTIR spectral overlay pure drug Metoprolol Tartrate (curve A), polymer HPMC K4M (curve B) and mixture of metoprolol tartrate and HPMC K4M (curve C).



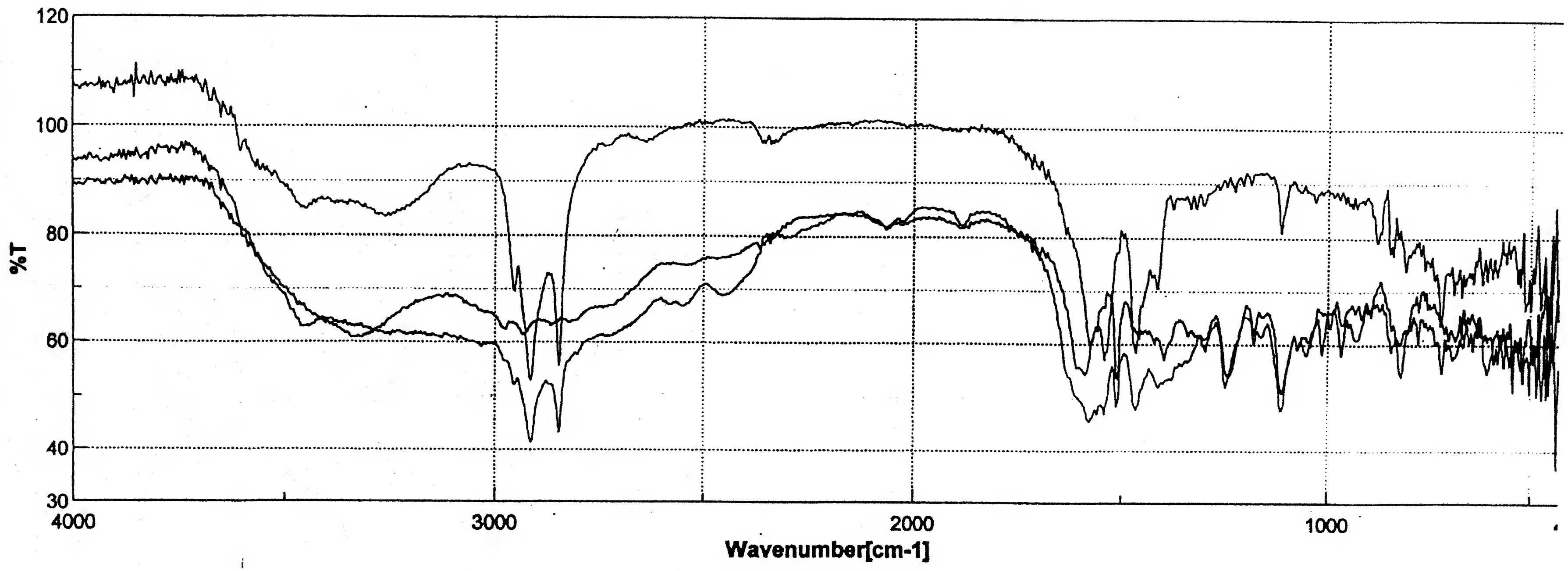
Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	Auto (64)	Scanning Speed	Auto (2 mm/sec)
Date/Time	1/18/05 4:45PM	Update	1/18/05 4:46PM
Operator	BM DINESH		
File Name	Metoprolol Tartrate + HPMC K100M		
Sample Name	drug mt		
Comment			

Fig. 8.13. FTIR spectral overlay pure drug Metoprolol Tartrate (curve A), polymer HPMC K100M (curve B) and mixture of metoprolol tartrate and HPMC K100M (curve C).



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	Auto (64)	Scanning Speed	Auto (2 mm/sec)
Date/Time	1/18/05 4:18PM	Update	2/5/05 0:29PM
Operator	BM DINESH		
File Name	Lactose		
Sample Name	drug mt		
Comment			

Fig. 8.14. FTIR spectral overlay pure drug Metoprolol Tartrate (curve A), diluent lactose (curve B) and mixture of metoprolol tartrate and lactose (curve C).



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	Auto (64)	Scanning Speed	Auto (2 mm/sec)
Date/Time	1/18/05 4:40PM	Update	1/18/05 4:42PM
Operator	BM DINESH		
File Name	Metoprolol Tartrate + Magnesium Stearate		
Sample Name	drug mt		
Comment			

Fig. 8.15. FTIR spectral overlay pure drug Metoprolol Tartrate (curve A), lubricant magnesium stearate (curve B) and mixture of metoprolol tartrate and magnesium stearate (curve C).

8.2. INSTRUMENTAL ESTIMATION

8.2.2. Standard Calibration Curve for Metoprolol Tartrate

As the absorbance for the series of concentrations were determined against the medium blank (pH 6.8 phosphate buffer) in which the drug is dissolved. From the statistical treatment[2] of the data (Table 8.5), it can be said that the curve is a straight line (correlation coefficient value = 0.9998), with slope 0.00357 (± 0.000047). The estimated average for intercept is 0.0084 (± 0.0036) which can be considered as Zero (Fig 8.18) i.e., to pass through the origin. Passing of the line through the origin implies that there are no interfering substances in the solution under study. It can be concluded that the Beer's Law is obeyed between ~0-280 μgm/mL for active substance metoprolol tartrate in pH 6.8 phosphate buffer solution under the defined experimental conditions carried out.

Table 8.5. Statistical values for the standard calibration curve for Metroprolol Tartrate in pH 6.8 phosphate buffer solution at 275 nm.

Metoprolol Tartrate (μgm/mL)	Replicate					
	1	2	3	4	5	6
25	0.0863	0.0863	0.0907	0.0895	0.0853	0.0877
50	0.1794	0.1823	0.1869	0.1847	0.1820	0.1820
75	0.2689	0.2759	0.2805	0.2746	0.2764	0.2792
100	0.3604	0.3742	0.3740	0.3671	0.3724	0.3754
125	0.4472	0.4580	0.4752	0.4662	0.4643	0.4651
150	0.5344	0.5468	0.5631	0.5564	0.5502	0.5575
175	0.6297	0.6360	0.6544	0.6416	0.6417	0.6535
200	0.7155	0.7234	0.7444	0.7347	0.7289	0.7416
225	0.8012	0.8086	0.8368	0.8192	0.8166	0.8204
250	0.8792	0.8881	0.8953	0.9071	0.9058	0.9113
275	0.9749	0.9769	0.9865	0.9948	0.9932	0.9993
300	1.0550	1.0657	1.0436	1.0792	1.0774	1.0971
Correlation Coefficient	0.9998	0.9998	0.9998	0.9998	0.9998	0.9998
Slope	0.00352	0.00353	0.00355	0.00360	0.00360	0.00364
Intercept	0.00517	0.01092	0.01447	0.00755	0.00650	0.00582

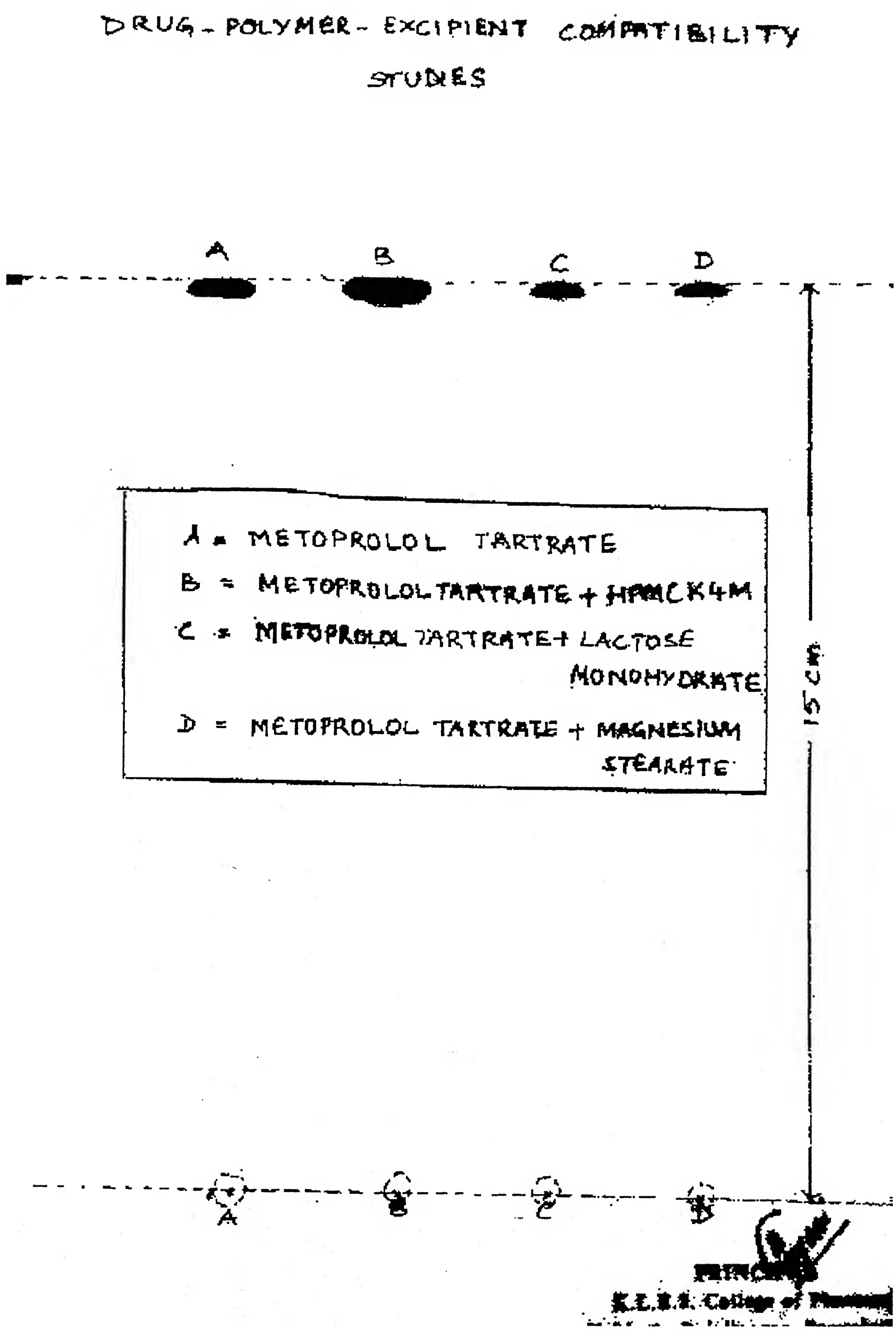


Fig. 8.16. Chromatogram for drug (metoprolol tartrate) and polymer (HPMC K 4M) and other excipients.

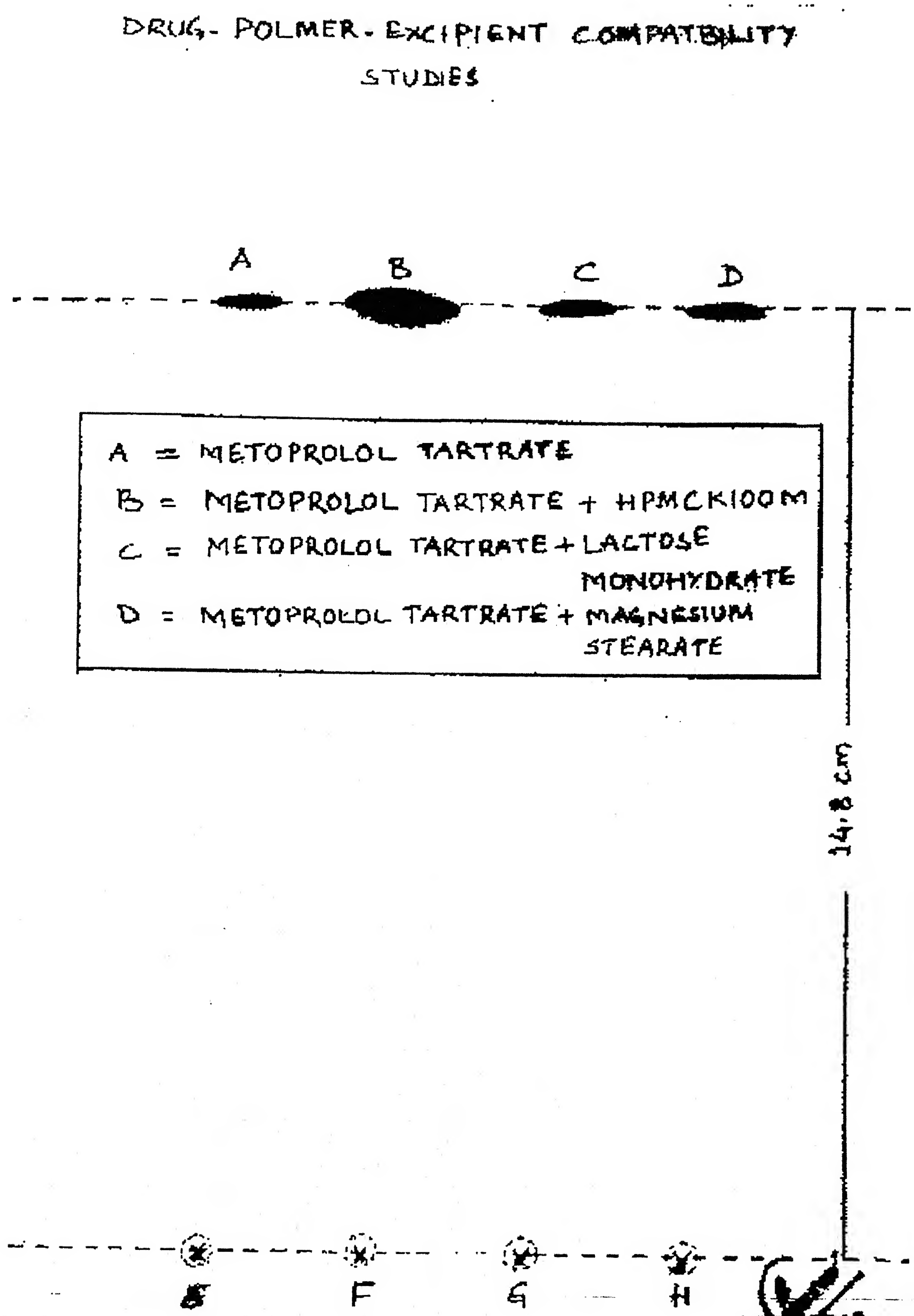


Fig. 8.17. Chromatogram for drug (metoprolol tartrate) and polymer (HPMC K 100M) and other excipients.

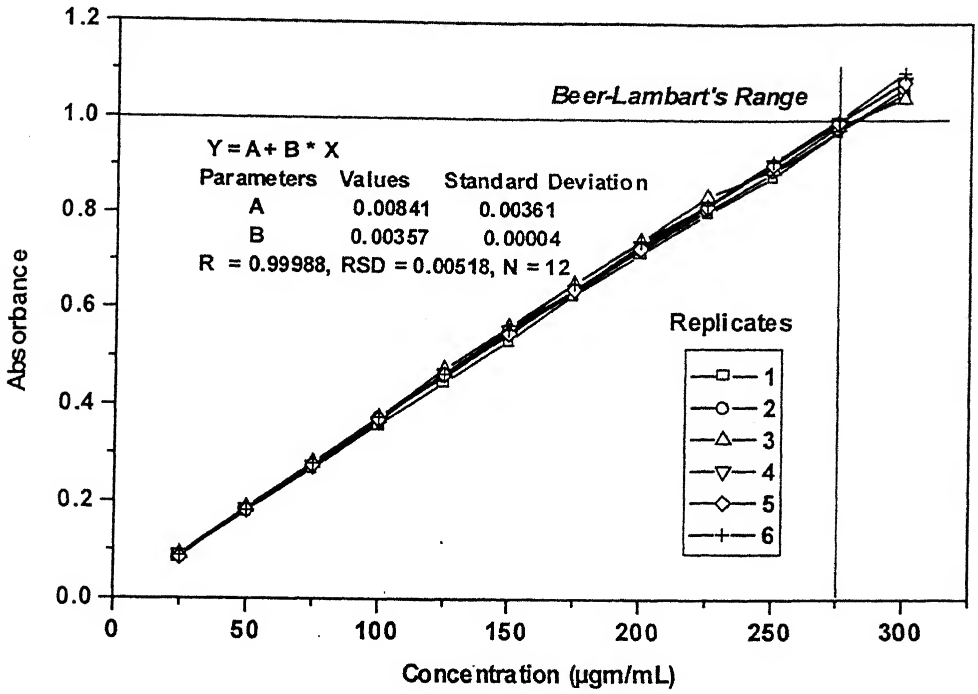


Fig.8.18. Metoprolol Tartrate standard calibration curve (275nm, pH 6.8 phosphate buffer).

8.2.3. Absorption stability of Active Substance – Metoprolol Tartrate

From the data given in Table 8.6 and fig. 8.19, it is observed that the active substance metoprolol tartrate absorption stability remains constant (as concluded from the small difference in the standard deviations) for the duration of study period (~3 days) in pH 6.8 phosphate buffer solution at 275 nm.

Table 8.6. UV-absorption spectral stability of metoprolol tartrate in pH 6.8 phosphate buffer solution at 275 nm.

Time (in hours)	% Content					
	Set 1	Set 2	Set 3	Set 4	Set 5	Set 6
2	100.00	100.00	100.00	100.00	100.00	100.00
4	99.99	99.99	99.98	99.99	99.97	99.98
8	99.99	99.99	99.99	99.97	99.98	99.97
24	99.99	99.99	99.98	99.97	99.99	99.99
46	99.98	99.98	99.98	99.98	99.97	99.97
72	99.98	99.98	99.97	99.98	99.98	99.97
Average	99.99	99.99	99.98	99.98	99.98	99.98
Standard Deviation	0.008	0.008	0.010	0.012	0.012	0.013

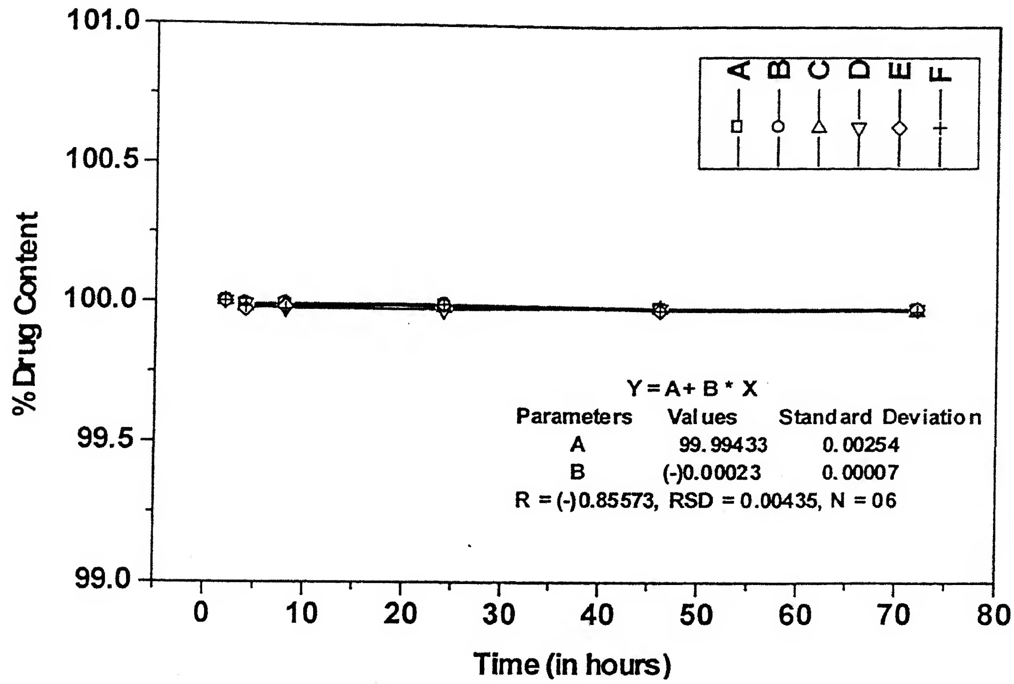


Fig. 8.19. Spectral stability of the drug in pH 6.8 phosphate buffer solution at 275nm.

8.3. ANALYTICAL METHOD AND ITS VALIDATION FOR METOPROLOL TARTRATE EXTENDED RELEASE TABLETS

8.3.1. Accuracy Study

- The results of accuracy study undertaken are given in Table 8.7. The % Recovery values show by spectrophotometric method show closeness of test results to the true values.

Table 8.7. Accuracy study.

Recovery Level	Drug Quantity added (mg)	% Recovery			SD	RSD
		Set 1	Set 2	Set 3		
1	25.0	98.56	98.68	98.28	0.385	0.390
2	37.5	99.28	99.39	99.81	0.280	0.281
3	50.0	100.16	99.72	98.60	0.804	0.808
4	62.5	99.57	99.73	98.92	0.429	0.432
5	75.0	100.84	100.06	99.56	0.645	0.644

8.3.2. Precision of Assay: The results of reported in the Table 7.8. From the low values of SD and RSD, it can be said that the there is high degree of agreement among the individual tests results when the method is applied repeatedly to multiple samples.

Table 8.8. Assay Precision

Set	% Label Claim						SD	RSD
1	99.33	99.51	100.03	99.44	100.29	100.41	0.491	0.491
2	99.37	99.24	100.62	99.81	100.51	100.20	0.580	0.581
3	99.42	99.24	99.33	99.36	99.28	99.22	0.076	0.077

8.3.3. Ruggedness for *in vitro* dissolution data: The method of analysis used in the *in vitro* dissolution studies is found to be sufficiently rugged (Table 8.9).

Table 8.9. Dissolution ruggedness.

Time (in hours)	% Cumulative Drug Release (No. of Samples = 6 per Set)				RSD
	Set I	Set II	Set III	Average	
1	28.73	27.05	27.89	27.89	3.01
4	68.81	67.78	69.13	68.57	1.03
8	86.65	86.17	86.80	86.54	0.38

8.3.4. Specificity: The data for the specificity of analytical method used is given in Table 7.10. The results indicate the spectrophotometric method used is reliable.

Table. 8.10. Specificity of analytical method.

S. No.	Standard with Placebo Value (I) (mg)		Standard without Placebo Value (II) (mg)	% Agreement between Value I & II
	Amount Added	Amount Found	Amount Found	
1	50.00	49.68	49.64	100.08
2	50.00	49.66	49.68	99.96
3	50.00	49.63	49.62	100.02
4	50.00	49.63	49.66	99.94
5	50.00	49.65	49.63	100.04
			Mean =	**100.06**
			SD = 0.06; RSD = 0.06	
Interference: No interference was observed.				

8.3.5. Limit of Detection (LOD) and Limit of Quantification: The LOD is found to be 1μgm/mL having the absorbance of 0.0036. Limit of Quantification was found to be 6μgm/mL (6 times of the detection). The results of concentration against absorbance are plotted (fig. 8.20).

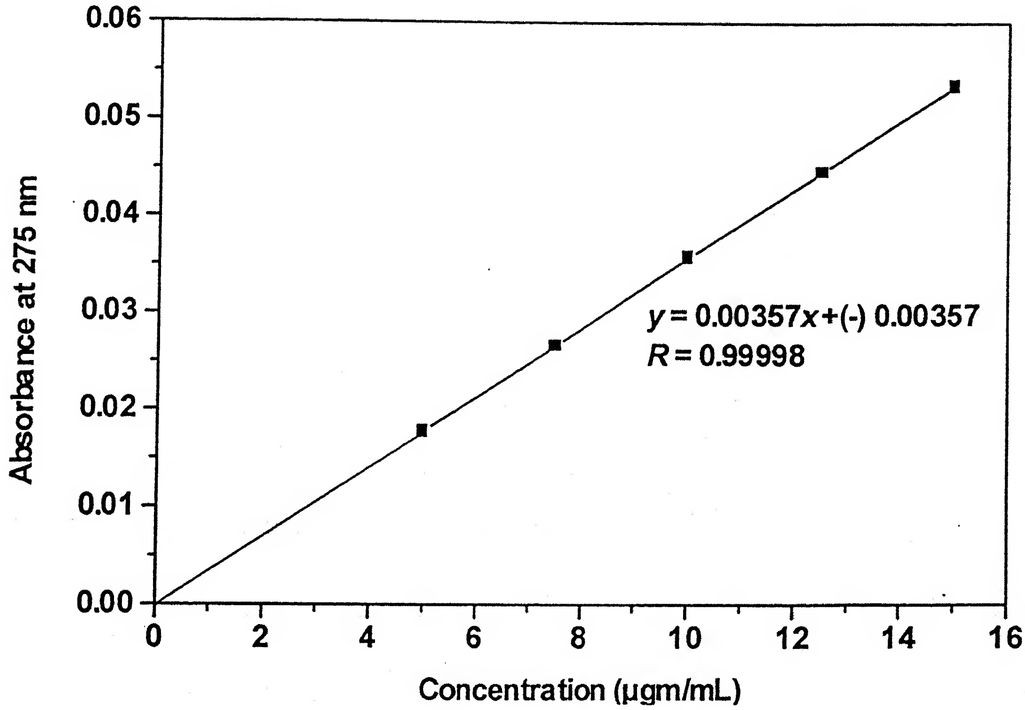


Fig.8.20. Linearity at 50% to 150% of Limit of Quantitation.

8.3.6. Linearity and Range: Plot of concentration of Metoprolol Tartrate against absorbance is shown in Fig. 8.18. The standard deviation of the experiment was found to 0.00361 and 0.00004.

8.4. EVALUATION OF FORMULATIONS

8.4.1. Unofficial Tests

The fabricated ER hydrophilic matrix tablets of MT in general were colorless, circular, biconvex; uniform in appearance and homogeneous in texture. There was no significant variation in the tablet properties even though there was change in the level

of polymer and the type. The values fluctuated between 9.033-9.075mm, 0.314-0.314mm for diameter and thickness respectively, 5.30-5.70 kg/cm^2 for hardness, 0.8473-0.4937 for friability, 109.42-110.21 for weight variation (% active content) and 109.01- 109.85 for Content Uniformity (Actual of active content). The disintegration time varied from 45 minutes and more; in some formulations the tablet remained un-disintegrated even after 24 hours. Details are given in Table 8.11 and 8.12.

Table 8.11. Dimensions, hardness and friability values in various formulations.

Formulation Code	Dimension		Hardness (kg/cm^2)	Friability (%)
	Diameter (mm)	Thickness (mm)		
A-1	9.060 (0.031)	3.317 (0.003)	5.65 (0.53)	0.8473
A-2	9.075 (0.015)	3.318 (0.002)	5.70 (0.25)	0.6781
A-3	9.030 (0.022)	3.314 (0,002)	5.40 (0.63)	0.6482
A-4	9.046 (0.026)	3.316 (3.002)	5.50 (0.15)	0.5817
A-5	9.063 (0.016)	3.315 (0.003)	5.35 (0.20)	0.5861
A-6	9.067 (0.046)	3.316 (0.002)	5.40 (0.15)	0.4937
B-1	9.066 (0.035)	3.320 (0.002)	5.50 (0.25)	0.5781
B-2	9.072 (0.013)	0.314 (0.003)	5.45 (0.35)	0.5482
B-3	9.033 (0.022)	3.316 (0.001)	5.50 (0.15)	0.6817
C-1	9.050 (0.025)	3.319 (0.002)	5.33 (0.15)	0.5861
C-2	9.064 (0.017)	3.321 (0.004)	5.30 (0.20)	0.7937

* Values in the parenthesis indicate the standard deviation estimated from 6 separate tablets.

Table 8.12. Various official tests values on the fabricated ER hydrophilic matrix system.

Formulation Code	Weight Variation (% Active Content)	Content Uniformity (Actual % Active Content)	Disintegration Test (hours)[a]
A-1	109.80 (0.56)[a]	109.01 (1.77)[a]	0.75[b]
A-2	110.04 (0.37)[a]	109.04 (0.97)[a]	2.0[b]
A-3	109.44 (0.28)[a]	109.57 (1.24)[a]	3.5[b]
A-4	109.55 (0.23)[a]	109.85 (2.01)[a]	5[b]
A-5	109.42 (0.42)[a]	109.42 (1.96)[a]	<12[b]
A-6	110.21 (0.46)[a]	109.04 (1.75)[a]	< 24[b]
B-1	111.04 (0.73)[a]	109.04 (1.17)[a]	11[b]
B-2	110.44 (0.58)[a]	109.57 (2.24)[a]	<12[b]
B-3	109.55 (0.27)[a]	109.85 (2.26)[a]	< 24[b]
C-1	109.42 (0.55)[a]	109.42 (2.59)[a]	< 12[b]
C-2	109.31 (0.42)[a]	109.42 (2.36)[a]	< 24[b]

- Values in the parenthesis indicate the standard deviation estimated from 10 separate tablets.
- [a]Average of the 6 separate tablets. Time recorded when no matrix was present present on the sieve, observed at and interval of 15 minutes.

The test results indicate that the MT ER tablets prepared from various formulations containing HPMC K4M and HPMC K100M control release polymer and its blends had satisfactory tablet properties and within the defined official limit specifications.

8.4.2. *In vitro* Release

The *in vitro* % cumulative release data for all the formulations prepared with low, high density polymers at various concentrations ~~and its~~ blend ~~compared~~ with the marketed reference listed drug Seloken XL 50 mg is given in Table 8.13 and the data plotted as cumulative release versus time is given in fig. 8.21, 8.22 and8. 23.

Table.8.13. In vitro release data of various laboratory developed ER Metoprolol Tartrate Tablet and RLD Seloken XL 50.

T^a	A-1	A-2	A-3	A-4	A-5	A-6	B-1	B-2	B-3	C-1	C-2	RLD^b
0	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
15	63.0061	25.3585	9.7208	5.4943	8.4296	5.1204	2.5359	6.0235	3.5530	5.2946	5.1901	2.2300
30	87.9479	35.9245	19.4415	7.1849	13.4107	7.8375	7.1849	12.5748	6.7730	8.4644	8.83594	4.5600
45	95.9396	44.3774	24.5132	18.5962	17.0338	9.6487	14.7925	14.8389	9.4398	11.1814	9.7532	6.3500
60	100.0000	51.1396	39.5983	22.8226	20.2031	12.3657	18.5962	17.5559	11.2510	13.4456	12.9966	8.3000
90		64.1115	48.4737	31.5681	24.7315	15.7446	26.4964	21.6314	15.3265	17.5210	16.9986	12.3682
120		73.8322	55.2360	40.0209	30.1655	19.3672	33.6813	26.6125	18.9492	21.1437	20.1684	15.3401
150		85.6662	61.1530	45.9379	35.1466	22.0842	38.7530	31.1408	22.1119	24.3135	24.2438	17.6600
180		89.8926	66.2247	51.4322	39.6749	24.9553	43.8247	34.3108	24.8360	27.9361	27.8664	20.1501
210		92.8511	71.2964	55.6586	43.2975	27.6923	48.0511	38.3860	26.6473	31.1060	30.1306	24.6308
240		96.6486	79.3266	60.3077	47.3730	29.8867	52.2775	41.1031	28.9115	33.8229	32.8476	27.6308
300		98.3454	85.6662	67.4926	53.8069	34.6937	59.4624	46.5370	32.5341	39.7097	37.3759	34.4900
360		100.0000	90.3152	73.8322	58.5637	39.3614	65.3794	51.5181	35.7039	44.6909	41.4514	41.5308
420			94.1190	78.9039	63.6947	43.2278	70.8737	56.0464	38.8737	49.2192	44.9695	48.2401
480			98.9681	83.5529	68.6560	47.1291	75.5228	60.5747	41.5907	53.2946	48.0000	56.2401
600			100.0000	90.3154	76.3541	53.5733	83.1301	67.8200	46.4657	60.5399	53.3296	67.9301
1440				100.0000	100.0000	87.0827	100.000	100.0000	66.9492	99.9709	71.5123	100.0000

T^a = time in minutes, RLD^b = Seleken XL 50 mg (Reference Listed Drug)

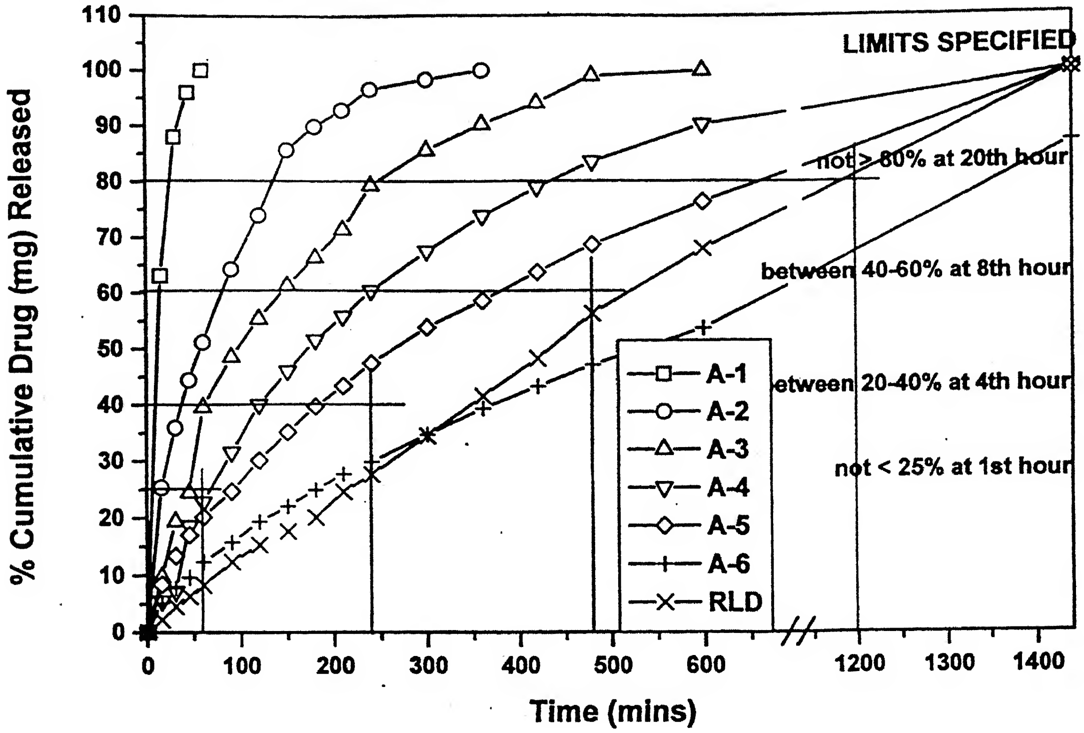


Fig. 8.21. *In vitro* release of Metoprolol tartrate from formulations prepared using HPMC K4M and RLD Seloken XL.

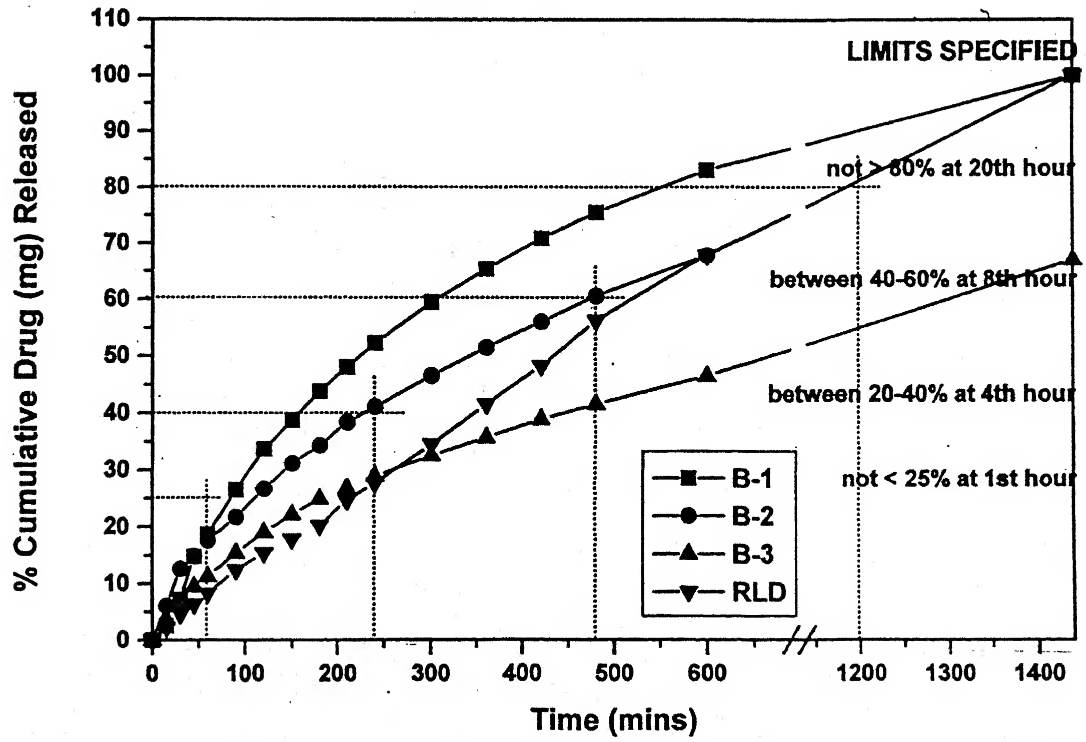


Fig. 8.2. *In vitro* release of Metoprolol tartrate from formulations prepared using HPMC K100M and RLD Seloken XL.

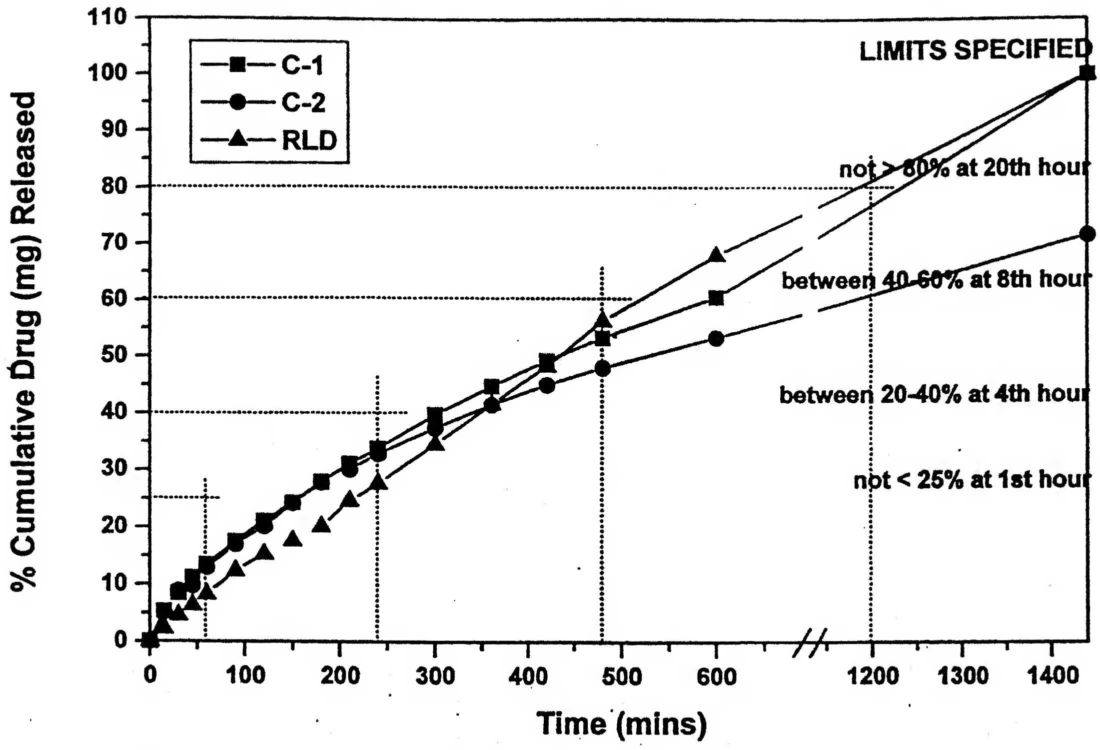


Fig. 8.23. *In vitro* release of Metoprolol tartrate from formulations prepared using blend of HPMC K4M & HPMC K100M and RLD Seloken XL.

8.5. LABORATORY PILOT BATCH

8.5.1. Effect of Granule Moisture Content on Tablet Properties

As per the Master Formula given in Table 7.4 (Section 7.B.6.2., Ch. 7.) and procedure (Section 7.B.6.3., Ch. 7.) granules containing MT for ER tablets were prepared. The level of moisture as described as described in Ch. 6., Section 6.5.6. greatly influences the tabletting properties and the tablet. An optimum concentration of moisture is desired in the tablets for good binding properties. If more moisture is present, then it softens the tablets, affects other properties like friability, chipping, capping, hardness, etc. The moisture content level therefore is critical and specific for a drug-polymer-excipient mixture; has a narrow range, need to be monitored to built-in desired properties in the tablet manufacture. Tests were performed to study the effect of moisture content on the tablet properties. The test and the results are given in Table 8.14.

Table 8.14. Effect of Moisture (LOD) on compressibility of Metoprolol Tartrate Extended Release Tablet (Pilot Batch D).

Parameters	Moisture Content (n = 3) at 90 ^oC (% w/w)			
	0.5 – 0.7	**1.5 – 1.7***	**2.6 – 2.8***	**3.8 – 4.2***
Capping	Not Present	Not Present	Not Present	Not Present
Sticking & Picking	Not Present	Not Present	Not Present	Not Present
Surface Appearance	Surface not smooth. Loose powder on the tablet.	Surface smooth. Loose powder on the tablet.	Surface smooth. Some loose powder on the tablet.	Surface smooth. No loose powder on the tablet.
Hardness (kg/cm^2)	3-4	3-5	4-6	5-6
Friability (% w/w)	1.9	1.45	1.2	0.9
* To the base granules with moisture content of 0.5 – 0.7%, additional moisture was incorporated to give the final moisture content.				

For the ingredients used and the method of preparation of MT ER tablets, the optimum moisture content under the present study is between 3.8 to 4.2 % w/w.

8.5.2. Effect of Temperature on Tablet Properties

Before subjecting the granules to tabletting, a sufficient quantity of granules were exposed for 7 days to the conditions along with the tests results are described in Table 8.15. *In vitro* dissolution studies were also performed (data -Table 8.16, plot – fig. 8.24). There was some considerable change in the tablet hardness, which increased the granules exposed to 60 ^oC for when for 7 days and them compressed.

Table 8.15. Evaluation of metoprolol tartrate extended release tablets (Pilot Batch D) compressed using granules exposed at 60 °C days and unexposed granules for 7 days.

S. No.	Test	Granules exposed at 60 °C	Unexposed granules at RT
1.	General Appearance		
1.1.	Shape	Circular	Circular
1.2.	Dimension (diameter, mm)	9.052 (±0.015)	9.056 (±0.018)
1.3.	Color	White	White
1.4.	Surface Texture	Smooth	Smooth
1.5.	Cracks and Pinholes	No	No
2.	Average Weight (mg)	252	251
3.	Weight variation (mg)	253 (± 0.003)	255 (± 0.005)
4.	Thickness (in mm)	3.319 (± 0.002)	3.321 (± 0.003
5.	Hardness (kg/cm^2)	6-7	5-6
6.	Friability (% w/w)	0.7	0.9
7.	Assay (%)	110.33 (± 1.36)	110.76 (± 1.92)

Table 8.16. *In vitro* release data for tablets (Pilot batch D) compressed from granules exposed to 60 °C and unexposed maintained at room temperature).

Time (in minutes)	Exposed at 60 °C	Unexposed at RT
0	0.0000	0.0000
15	5.3147	5.3161
30	8.6621	8.6615
45	11.3812	11.1024
60	13.5452	13.4150
90	17.7211	17.3694
120	21.2659	21.1430
150	24.6197	24.3251
180	28.6264	27.9306
210	31.1060	31.1060
240	34.4218	33.9158
300	40.1689	39.8000
360	44.9183	44.8291
420	49.9183	49.3182
480	53.8248	53.3182
600	61.6338	60.9186
1440	100.0000	100.0000

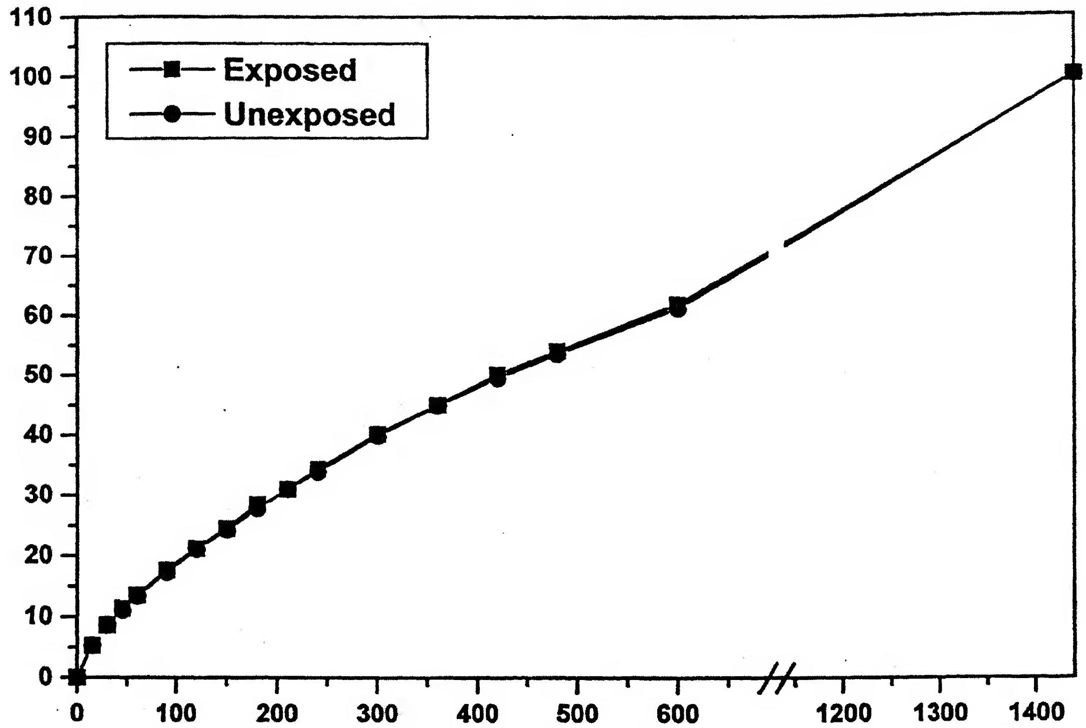


Fig. 8.24. % Cumulative release of Metoprolol Tartrate from ER compressed tablets exposed (60°C) and unexposed at RT granules for 7 days.

8.5.3. Effect of Temperature and Moisture on Granules and Tablets

The granules and the tablets were separately exposed at 40°C/ 75% RH and 8-10°C/ 60% RH for 1-7 days and the properties studied along with the test results, are given in Table 8.17 along with the tests reports.

Table 8.17. Exposure studies for Metoprolol Tratrate ER Granules and Tablets (Pilot Batch D).

Time	Exposure Studies at 40°C/ 75% RH	
	Granules	Tablets
1 Day	White, free flowing.	White, no changes observed.
7 Days	White, lumps in the granules, hindered flow.	White, no changes observed.
Hardness (kg/cm^2)	-	Initial = 5 - 7
		After 7 days = 3.5 – 5.5
LOD	Initial @ 40 °C/ 75% RH = 3.39%	Initial @ 40 °C/ 75% RH = 3.11%
	After 7 days @ 40 °C/ 75% RH = 4.15%	After 7 days @ 40 °C/ 75% RH = 3.63%
Assay	Initial = 106.89%	Initial = 106.90%
	After 7 days = 103.39%	After 7 days = 106.73%

The granules picked up comparatively more moisture to tablets, due to its increased surface area but within desired moisture content for tablets (between 3.8-4.2 %). However, this affected its flow properties. The hardness of the tablets was also reduced when the period was extended to 7 days compared to day 1 by almost 2 kgs

Samples kept under refrigeration (8-10 ^{O}C/ 60% RH), did not show any changes, at the end of 7 days study period, except the LOD values increased marginally. Therefore the results are not given here.

8.6. PILOT BATCH TABLET PROPERTIES

The average values of the tests results for granules and compressed matrix tablets for the pilot batch D (repeated thrice) are reported in Table 8.18 and 8.19.

Table 8.18. Granule characteristics of Metoprolol Tartrate prepared by wet granulation for Pilot Batch D.

Un-lubricated Granule Characteristics		
Parameters		**Average Values (n = 3)**
Loss on drying		4.01 % w/w @ 90^{O}C
% Fines		45
Lubricated Granule Characteristics		
Parameters		**Values**
Loss on drying		3.56 % w/w @ 90^{O}C
Particle Size Distribution		
Particle Size Distribution	# 18 - 30	29.32 % w/w
	# 30 - 60	26.33 % w/w
	# 60 - 80	16.45 % w/w
	Below # 80	27.90 % w/w
Untapped Bulk Density (gm/cm^2)		0.48
Tapped Bulk Density (gm/cm^2)		0.58
Carr's Index		1.20
Hausner Ratio		16.95
Angle of Repose		39^{O}42'
Assay		100.98 % w/w

Table 8.19. Evaluation of Pilot scale-up batch (D) for ER Metoprolol Tartrate 50 mg.

S. No.	Tests	Values	
1.	General Appearance	Uniform in appearance and homogeneous in texture.	
1.1.	Shape	Circular, biconvex.	
1.2.	Dimension (in mm)	9.052 (± 0.015) in diameter and 3.319 (± 0.002) in thickness.	
1.3.	Color	Colorless.	
1.4.	Surface Texture	Smooth.	
1.5.	Cracks and Pinholes	No	
2.	Average Weight	251 mg	
3.	Weight Variation	± 0.002 mg	
4.	Thickness	0.320 (± 0.004) mm.	
5.	Hardness	5.33 (± 0.15) kg/cm^2	
6.	Friability	0.5861 %	
7.	Content	109.42 (± 2.59)	
8.	In Vitro Dissolution	Observed Values	In House Range#
	At the end of 1st hour	14.1847 %	Not more than 25 %
	At the end of 4th hour	35.3228 %	Between 20-40 %
	At the end of 8th hour	54.6622%	Between 40-60 %
	At the end of 24th hour	Not done.	Not less than 95%

Based on the USP specifications.

8.7. ACCELERATED STABILITY STUDIES

8.7.1. Accelerated Stability Test Data

The various parameters tested and the data for accelerated stability study are given in Table 8.20.

Table 8.20. Short term accelerated stability evaluation test data for Metoprolol Tartrate ER tablets (Pilot Batch D).

Conditions	Initial	30 °C/ 65% RH			40 °C/ 75% RH		
		1 month	2 month	6 month	1 month	2 month	6 month
Appearance (Pack)	Clear Transparent Blister Pack	No Change	No Change	No Change	No Change	No Change	No Change
Appearances (Tablet)	White, Round	No Change	No Change	No Change	No Change	No Change	No Change
Average Weight (mg)	251.05	251.06	251.06	251.07	251.06	251.07	251.06
Uniformity of Weight (mg)	251.03 – 251.07	In limits	In limits	In limits	In limits	In limits	In limits
Thickness (mm)	0.320	In limits	In limits	In limits	In limits	In limits	In limits
LOD (% w/w)	3.1111	3.4012	3.3331	3.5956	3.2626	3.1919	3.6836
Friability (% w/w)	0.56	0.7071	0.6256	0.5136	0.7782	0.5535	0.0536
Assay (%)	101.23	102.62	101.45	100.55	101.19	100.43	101.73
Dissolution	No significant change in the dissolution profile was observed.						

8.7.2. *In vitro* dissolution Evaluation for assessing the effect of accelerated stability storage conditions

No significant changes occurred in physical and chemical parameters of the tablets after storing under accelerated stability conditions. The *in vitro* dissolution data (Table 8.21) and profile of ER metoprolol tartrate (Batch D) at the end of 6 month study period is shown in fig. 8.25.

Table 8.21. Cumulative % dissolution data of pilot batch D, after storage at accelerated stability conditions.

Time (in minutes)	Accelerated Storage Conditions		
	Initial	30^{o}C, 65 % RH	40^{o}C, 75 % RH
0	0.0000	0.0000	0.0000
15	5.2946	5.3147	8.6438
30	8.4644	8.6621	11.8155
45	11.1814	11.3812	14.8131
60	13.4456	13.5452	16.6255
90	17.521	17.7211	20.7034
120	21.1437	21.2659	24.3286
150	24.3135	24.3351	27.5132
180	27.9361	28.6264	31.1248
210	31.106	31.1060	33.8435
240	33.8229	34.4218	36.5621
300	39.7097	39.1852	42.9055
360	44.6909	44.9183	47.8897
420	49.2192	49.9183	52.8739
480	53.2946	53.8248	57.4049
600	60.5399	61.6338	64.6546
1440 (at T∞)	99.9707	100.0000	100.000

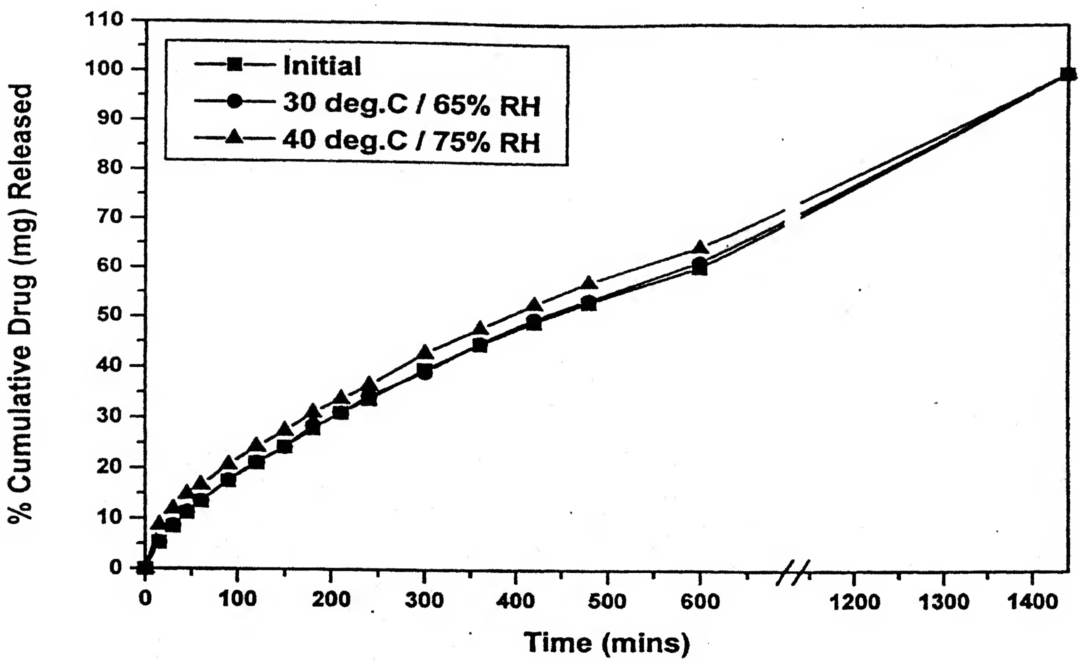


Fig. 8.25. Dissolution profile of metoprolol tartrate ER tablet (Batch D) after storage under accelerated stability conditions.

8.8. SWELLING STUDIES

8.8.1. Photographic Images

The photographs of Pilot Batch D were taken. The uniformed colored, round tablets (Fig. 8.26, A) and stratified texture in the broken section of the tablet (Fig. 8.26, B) is seen. Swelling study photographs (Fig. 8.27, C and 8.27, D) were taken at 2 hours hydration and a cross section at the end of 24 studies, under **static swelling conditions.** In photograph, formation of gel layer formed on the tablet can be distinctly seen and the longitudinal section of the swollen tablet matrix still contains some white scattered specks of dry, un-hydrated core in the centers still opaque indicating the penetration of solvent into the core is not complete. The core was found to be partially **dry and loose matrix** when the matrix tablet was longitudinal cut after 8 hours (photograph of which is not taken). Photograph 8.27 (B) shows anisotropic swelling of the tablet while the longitudinal section shows the core to be partially gelled at the end of 24 hours.

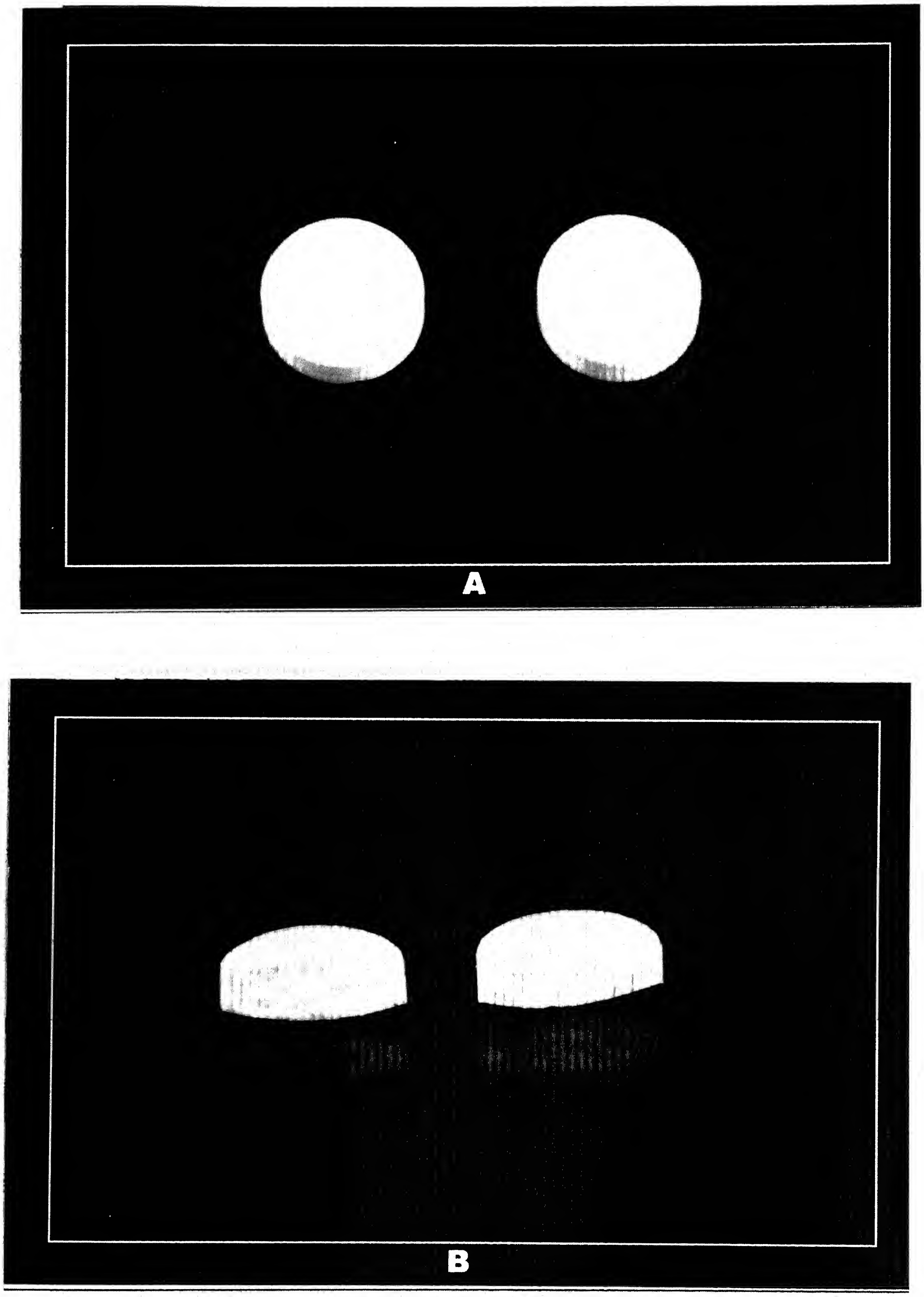


Fig. 8.26. Optical image of ER metoprolol tartrate compressed matrix tablet (pilot batch D), whole (A) and broken surface (B).

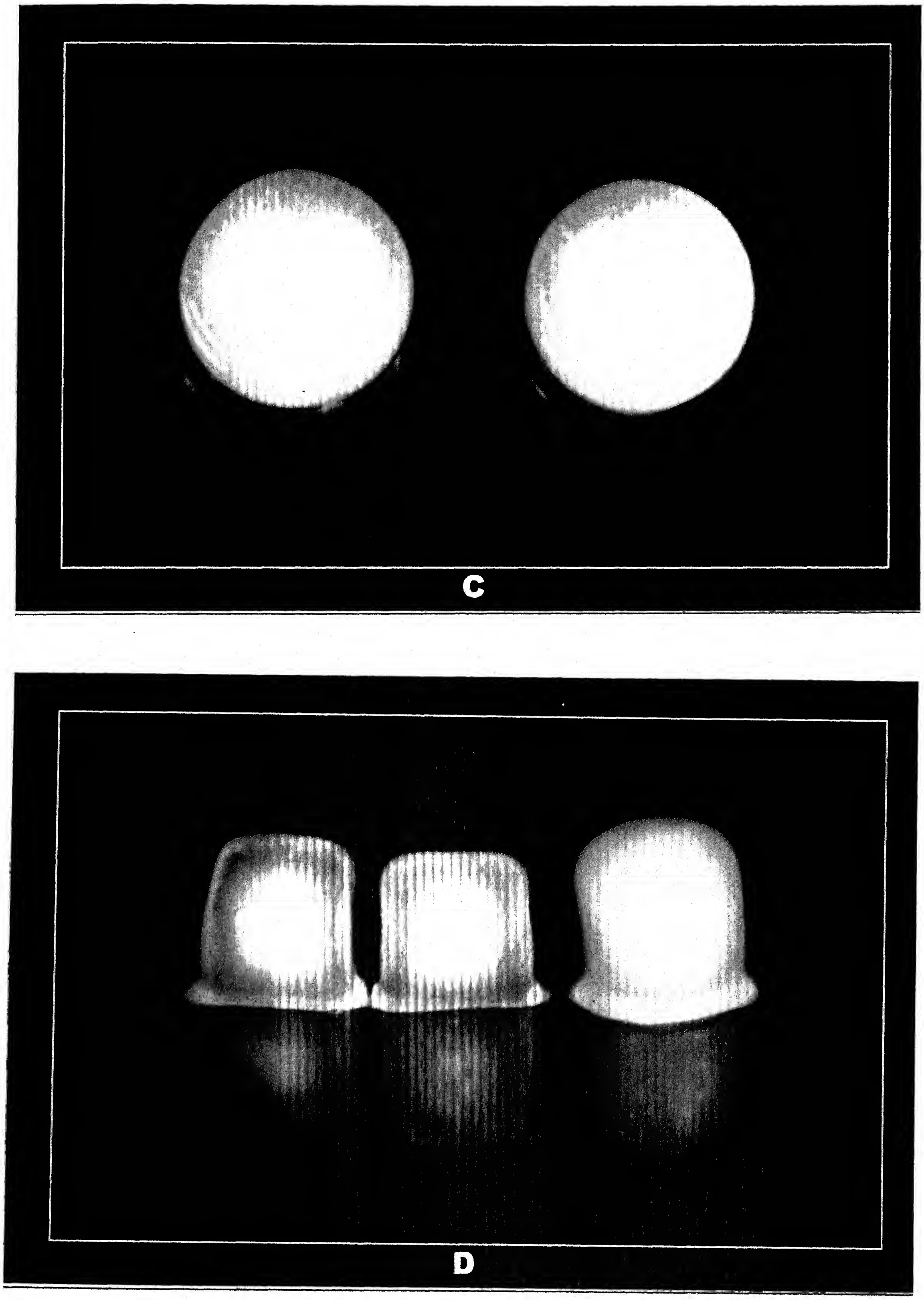


Fig. 8.27. Optical image of ER metoprolol tartrate (pilot batch D) undergoing swelling at t = 3 hours (C) and 24 hours (D).

8.8.2. Dimensional Changes Under Static Hydration Conditions

The change in the dimensions due to sorption of water at room temperature, under static conditions in radial and axial directions and the corresponding change in the normalized radial and axial directions are given in Table 8.22.

Table 8.22. Dimensional swelling of tablet under static condition.

Time (in mins)	Swelling Dimension (in mm)		Normalized Dimension	
	Radial	Axial	Radial	Axial
0	9.052	3.319	1.000	1.000
15	10.951	4.401	1.210	1.326
30	11.331	5.381	1.252	1.621
45	11.713	5.892	1.294	1.775
60	11.851	6.403	1.309	1.929
90	12.345	7.333	1.364	2.209
120	12.598	7.793	1.392	2.348
150	12.813	8.402	1.415	2.531
180	12.939	8.913	1.429	2.685
210	13.066	9.285	1.443	2.798
240	13.192	9.564	1.457	2.882
300	13.321	10.215	1.472	3.078
360	13.446	10.633	1.485	3.204
420	13.573	11.052	1.499	3.330
480	13.701	11.377	1.514	3.428
600	13.827	11.982	1.528	3.610
1440 (at T∞)	14.026	12.679	1.549	3.820

Fig. 8.28. shows the normalized dimensional changes of the pilot batch D under static conditions of swelling. Anisotropic swelling is obvious as the tablet axial length increases substantially over time, while the radial diameter remains fairly constant[3-7]. As the tablet matrix swells, tablet dimension in both the axial and radial directions constantly change, so that the path length in either directions varies as a function of time.

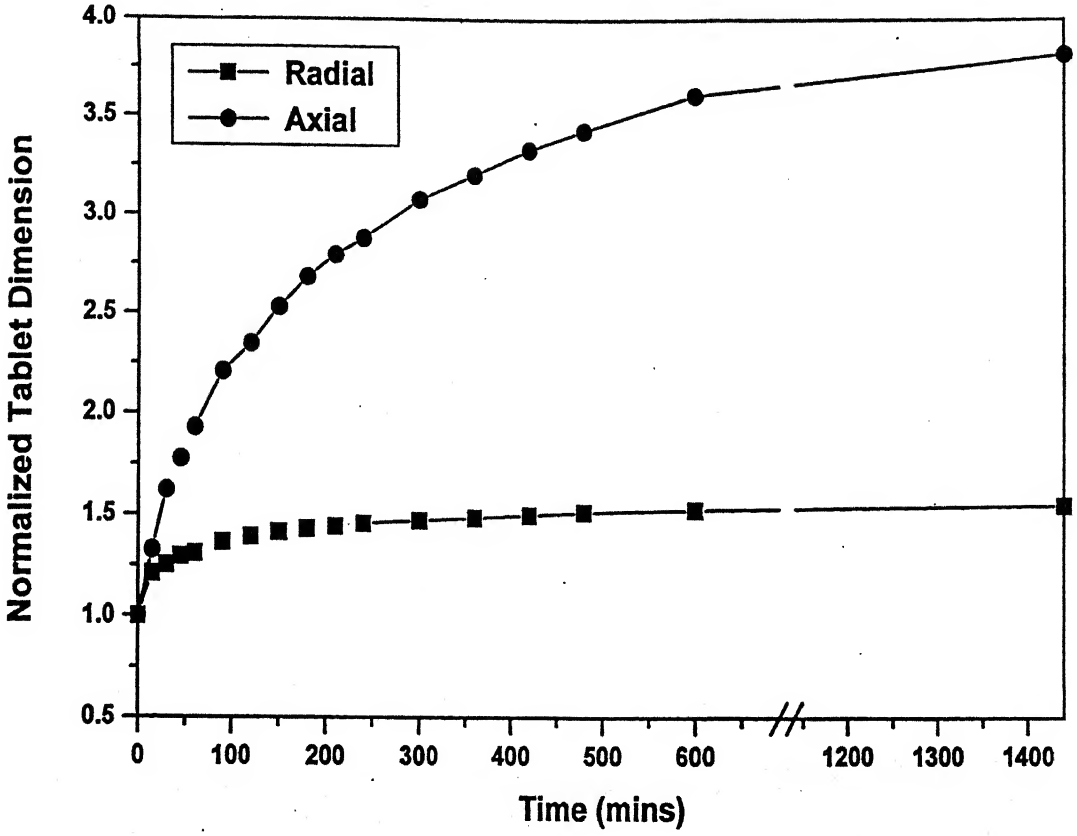


Fig. 8.28. Normalized radial and axial tablet dimensions of the swelling matrix tablet (pilot batch D).

8.9. MATHEMATICAL MODELS FOR RELEASE KINETICS

The *in vitro* release data obtained for the pilot batch (D), formulation optimization batch (C-1) were treated for various model curve fitting equations (Table 8.22, 8.23 and 8.24) and plotted. The linear regression parameters in each case are also determined.

Table 8.23. In vitro release and mathematical modeling data for Pilot Batch D.

T^a	CAoDR^b	GDR^c	% CDR^d	% CDU^e	Log % CDU^e	$^2\sqrt{T^a}$	$^3\sqrt{(FDU)^f}$	Log T^a	M_t/M_∞	Log M_t/M_∞
0	0.0000	0.0000	0.0000	100.0000	2.0000	0.0000	1.0000	---------	0.0000	-------
15	3.3460	3.3460	6.0889	93.9111	1.9727	3.8730	0.9793	1.1761	0.0609	-1.2154
30	4.5815	1.2355	8.3372	91.6628	1.9622	5.4772	0.9714	1.4771	0.0834	-1.0788
45	6.5589	1.9774	11.9357	88.0643	1.9448	6.7082	0.9585	1.6532	0.1194	-0.9230
60	7.7948	1.2359	14.1847	85.8153	1.9336	7.7460	0.9503	1.7782	0.1418	-0.8483
90	10.0191	2.2243	18.2324	81.7676	1.9126	9.4868	0.9351	1.9542	0.1823	-0.7392
120	12.2433	2.2242	22.2799	77.7201	1.8905	10.9545	0.9194	2.0792	0.2228	-0.6521
150	14.2205	1.9772	25.8780	74.1220	1.8699	12.2474	0.9050	2.1761	0.2588	-0.5870
180	16.1772	1.9567	29.4387	70.5613	1.8486	13.4164	0.8903	2.2553	0.2944	-0.5311
210	17.6806	3.4601	32.1746	67.8254	1.8314	14.4913	0.8786	2.3222	0.3217	-0.4925
240	19.4106	3.2334	35.3228	64.6772	1.8108	15.4919	0.8648	2.3802	0.3532	-0.4520
300	22.3764	2.9658	40.7198	59.2802	1.7729	17.3205	0.8400	2.4771	0.4072	-0.3902
360	25.0951	2.7187	45.6672	54.3328	1.7351	18.9737	0.8160	2.5563	0.4567	-0.3404
420	28.0608	2.9657	51.0641	48.9359	1.6896	20.4939	0.7880	2.6232	0.5106	-0.2920
480	30.0380	1.9772	54.6622	45.3378	1.6565	21.9089	0.7682	2.6812	0.5466	-0.2623
600	34.9811	4.9431	63.6574	36.3426	1.5604	24.4949	0.7136	2.7782	0.6366	-0.1961
1440 (T_∞)	54.9521	19.9710	100.0000	0.0000	0.0000	37.9473	0.0000	3.1584	1.0000	0.0000

T^a = Time (in mins); CAoDR^b = Cumulative Amount of Drug Released (in mg); GDR^c = Gradient Drug Released (in mg); CDR^d = Cumulative Drug Release; CDU^e = Cumulative Drug Unreleased, FDU^f = fraction of drug unreleased.

Table 8.24. In vitro release and mathematical modeling data for Batch C-1.

T^a	$CAoDR^b$	GDR^c	% CDR^d	% CDU^e	Log % CDU^e	$^2\sqrt{T^a}$	$^3\sqrt{(FDU)^f}$	Log T^a	M_t/M_∞	Log M_t/M_∞
0	0.0000	0.0000	0.0000	100.0000	2.0000	0.0000	1.0000	---------	0.0000	-----------
15	2.9103	2.9103	5.2946	94.7054	1.9764	3.8730	0.9820	1.1761	0.0529	-1.2765
30	4.6527	1.7424	8.4644	91.5356	1.9616	5.4772	0.9709	1.4771	0.0846	-1.0726
45	6.1462	1.4935	11.1814	88.8186	1.9485	6.7082	0.9612	1.6532	0.1118	-0.9516
60	7.3908	1.2446	13.4456	86.5544	1.9373	7.7460	0.9530	1.7782	0.1345	-0.8713
90	9.6308	2.2400	17.5210	82.4790	1.9163	9.4868	0.9378	1.9542	0.1752	-0.7565
120	11.6223	1.9915	21.1437	78.8563	1.8968	10.9545	0.9238	2.0792	0.2114	-0.6749
150	13.3647	1.7424	24.3135	75.6865	1.879	12.2474	0.9113	2.1761	0.2431	-0.6142
180	15.3560	1.9913	27.9361	72.0639	1.8577	13.4164	0.8965	2.2553	0.2794	-0.5538
210	17.0984	1.7424	31.1060	68.8940	1.8382	14.4913	0.8832	2.3222	0.3111	-0.5071
240	18.5918	1.4934	33.8229	66.1771	1.8207	15.4919	0.8714	2.3802	0.3382	-0.4708
300	21.8277	3.2359	39.7097	60.2903	1.7802	17.3205	0.8448	2.4771	0.3971	-0.4011
360	24.5658	2.7381	44.6909	55.3091	1.7428	18.9737	0.8209	2.5563	0.4469	-0.3498
420	27.0549	2.4891	49.2192	50.9708	1.7073	20.4939	0.7988	2.6232	0.4922	-0.3079
480	29.2951	2.2402	53.2946	46.7054	1.6694	21.9089	0.7759	2.6812	0.5329	-0.2734
600	33.2777	3.9826	60.5399	39.4601	1.5916	24.4949	0.7735	2.7782	0.6054	-0.2180
1440 (T_∞)	54.9521	21.6744	99.9707	0.0293	0.0000	37.9473	0.0664	3.1584	0.9997	-0.0001

T^a = Time (in mins); $CAoDR^b$ = Cumulative Amount of Drug Released (in mg); GDR^c = Gradient Drug Released (in mg); CDR^d = Cumulative Drug Release; CDU^e = Cumulative Drug Unreleased, FDU^f = fraction of drug unreleased.

Table 8.25. In vitro release and mathematical modeling data for Seloken XL50.

T^a	CAoDR^b	GDR^c	% CDR^d	% CDU^e	Log % CDU^e	$^2\sqrt{T^a}$	$^3\sqrt{(FDU)^f}$	Log T^a	M_t/M_∞	Log M_t/M_∞
0	0.0000	0.0000	0.0000	100.0000	2.0000	0.0000	1.0000	---------	0.0000	-----------
15	1.2254	1.2254	2.2300	97.7700	1.9902	3.8730	0.9925	1.1761	0.0223	-1.6517
30	2.5057	1.2804	4.5600	95.4400	1.9797	5.4772	0.9846	1.4771	0.0456	-1.3410
45	3.4893	0.9836	6.3500	93.6500	1.9715	6.7082	0.9784	1.6532	0.0635	-1.1972
60	4.5608	3.5772	8.3000	91.7000	1.9624	7.7460	0.9715	1.7782	0.0830	-1.0809
90	6.7863	2.2255	12.3682	89.6318	1.9525	9.4868	0.9569	1.9542	0.1237	-0.9076
120	8.4293	1.6430	15.3401	84.6599	1.9277	10.9545	0.9460	2.0792	0.1534	-0.8142
150	9.7041	1.2748	17.6600	82.3400	1.9156	12.2474	0.9373	2.1761	0.1766	-0.7530
180	11.0724	1.3683	20.1501	79.8499	1.9023	13.4164	0.9277	2.2553	0.2015	-0.6957
210	13.1958	2.1234	24.0144	75.9856	1.8807	14.4913	0.9125	2.3222	0.2401	-0.6196
240	15.1830	4.1106	27.6308	72.3692	1.8596	15.4919	0.8978	2.3802	0.2763	-0.5586
300	18.9521	3.7691	34.4900	65.5100	1.8163	17.3205	0.8685	2.4771	0.3449	-0.4623
360	22.8210	3.8689	41.5308	58.4692	1.7669	18.9737	0.8362	2.5563	0.4153	-0.3816
420	26.8264	4.0054	48.8200	51.1800	1.7091	20.4939	0.7999	2.6232	0.4882	-0.3114
480	30.9037	4.0773	56.2401	43.7599	1.6411	21.9089	0.7592	2.6812	0.5624	-0.2500
600	37.3273	6.4236	67.9301	32.0699	1.5061	24.4949	0.6845	2.7782	0.6793	-0.1679
1440 (T_∞)	54.9496	17.6223	100.0000	0.0000	0.0000	37.9473	0.0000	3.1584	1.0000	0.0000

T^a = Time (in mins); CAoDR^b = Cumulative Amount of Drug Released (in mg); GDR^c = Gradient Drug Released (in mg); CDR^d = Cumulative Drug Release; CDU^e = Cumulative Drug Unreleased, FDU^f = fraction of drug unreleased.

8.9.1. Gradient Release Model

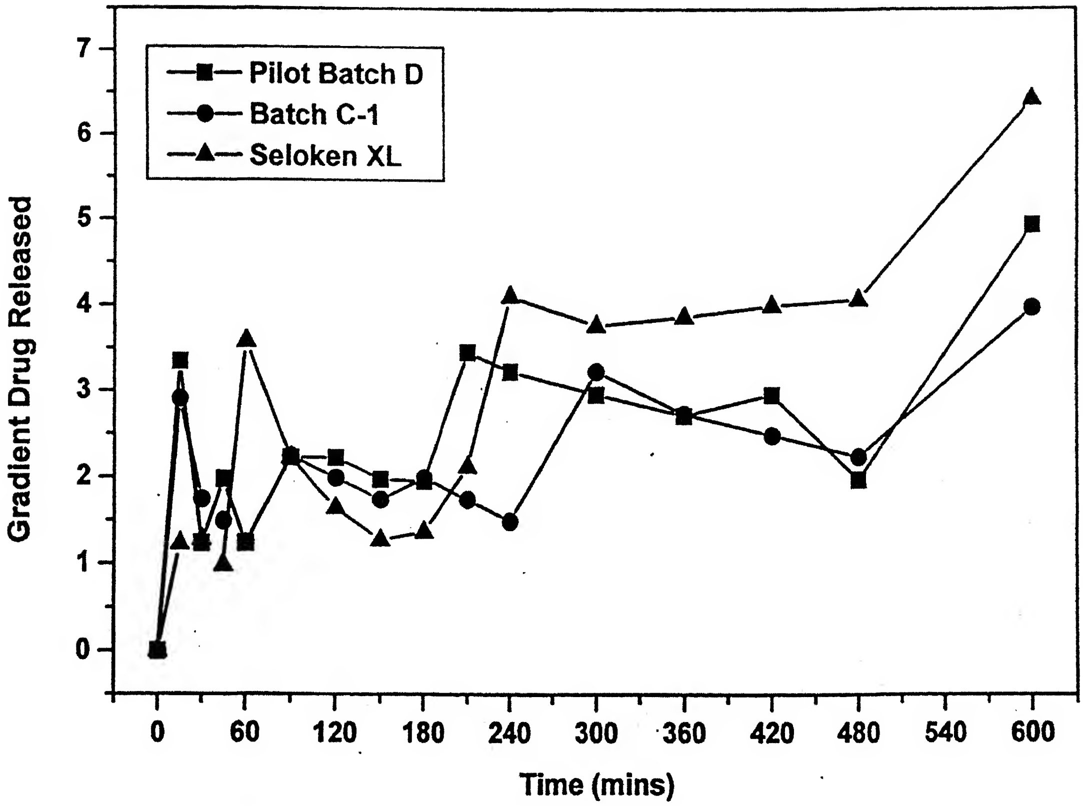


Fig. 8.29. Gradient of drug released versus time.

8.9.2. Zero Order Model

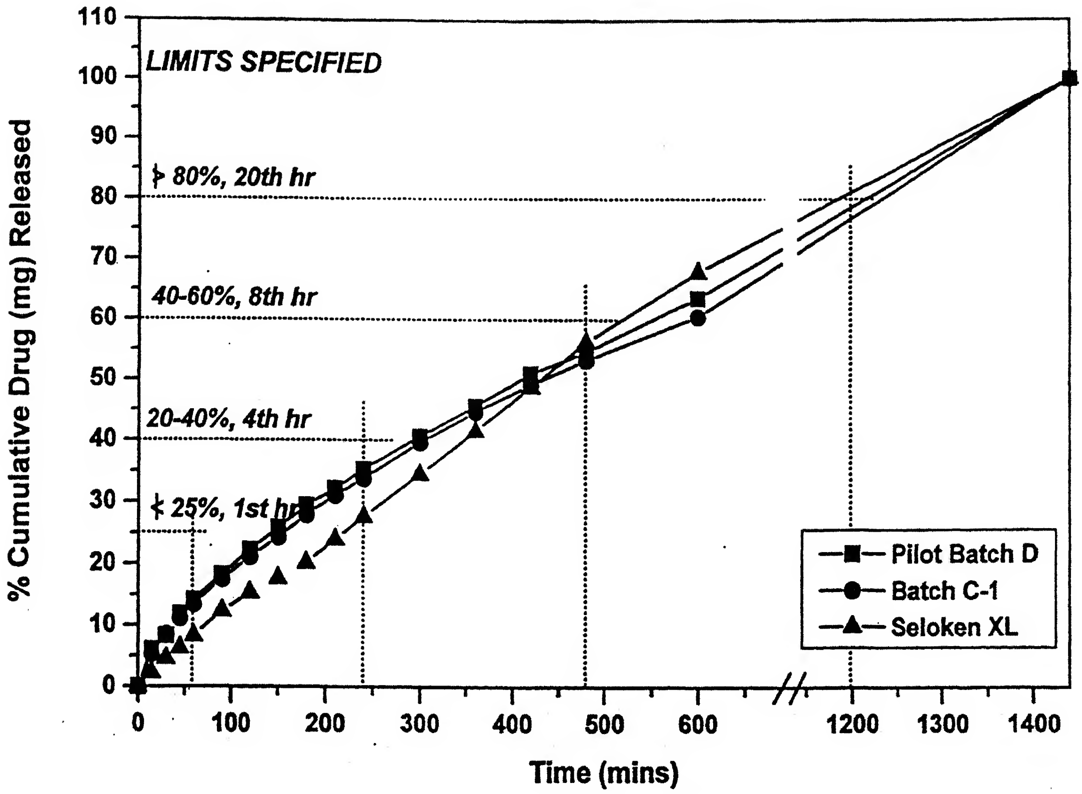


Fig. 8.30. Zero Order release kinetic plot.

Table 8.26. Linear regression parameters for zero order release.

Product	Linear ($y = A + Bx$) Regression Parameter Values				
	A *(intercept)*	*B* *(Slope)*	R (Regression Coefficient)	SD (Standard Deviation)	N (Number of data points)
Pilot Batch D	4.2151 (0.7186)	0.0561 (0.0027)	0.9847	1.8615	16
Batch C-1	3.9748 (0.7051)	0.0543 (0.0026)	0.9843	1.8066	16
Seloken XL	0.5238 (0.1583)	0.0620 (0.0006)	0.9994	0.4100	16
Value in the parenthesis is the standard deviation.					

8.9.3. First Order Model

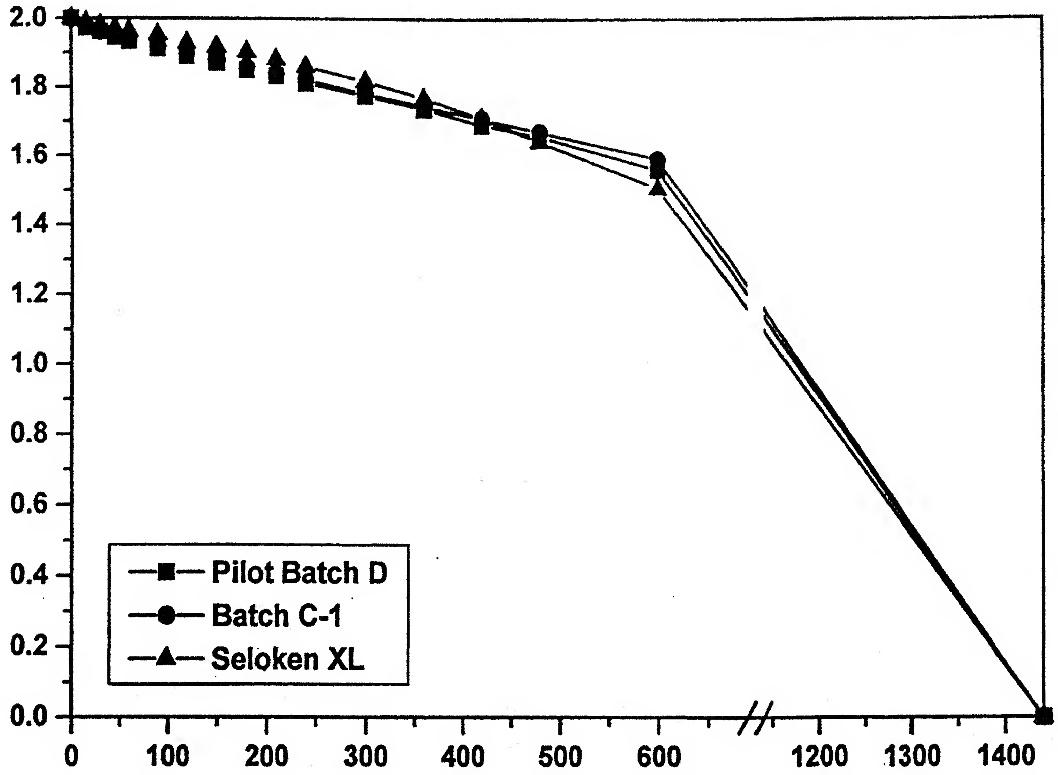


Fig. 8.31. First Order release kinetic plot.

Table 8.27. Linear regression parameters for first order release.

Product	Linear ($y = A + Bx$) Regression Parameter Values				
	A (*intercept*)	*B* (*Slope*)	R (Regression Coefficient)	SD (Standard Deviation)	N (Number of data points)
Pilot Batch D	1.9801 (0.0028)	-0.00069 (0.00001)	-0.99843	0.00728	16
Batch C-1	1.98064 (0.00253)	-0.00066 (9.34×10^6	-0.99859	0.00655	16
Seloken XL	2.02016 (0.0088)	-0.00077 (0.00003)	-0.98775	0.02279	16
Value in the parenthesis is the standard deviation.					

8.9.4. Higuchi Model

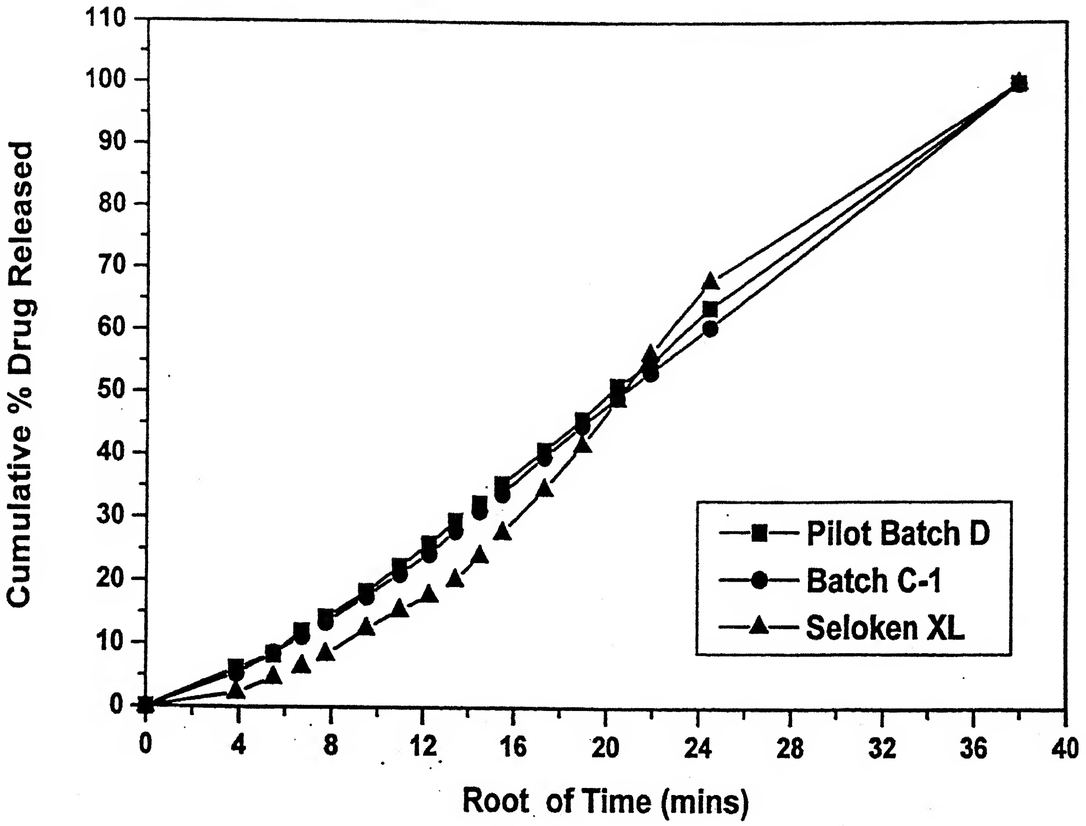


Fig. 8.32. Higuchi plot.

Table 8.28. Linear regression parameters for Higuchi model release

Product	Linear ($y = A + Bx$) Regression Parameter Values				
	A *(intercept)*	*B* *(Slope)*	R (Regression Coefficient)	SD (Standard Deviation)	N (Number of data points)
Pilot Batch D	-6.06587 (0.96624)	2.74969 (0.05787	0.99669	2.10439	17
Batch C-1	-6.73162 (1.06939)	2.72201 (0.06404)	0.99587	2.32906	17
Seloken XL	-12.6086 (2.52262)	2.91232 (0.15107)	0.98041	5.49409	17
Value in the parenthesis is the standard deviation.					

8.9.5. Hixon-Crowell Model

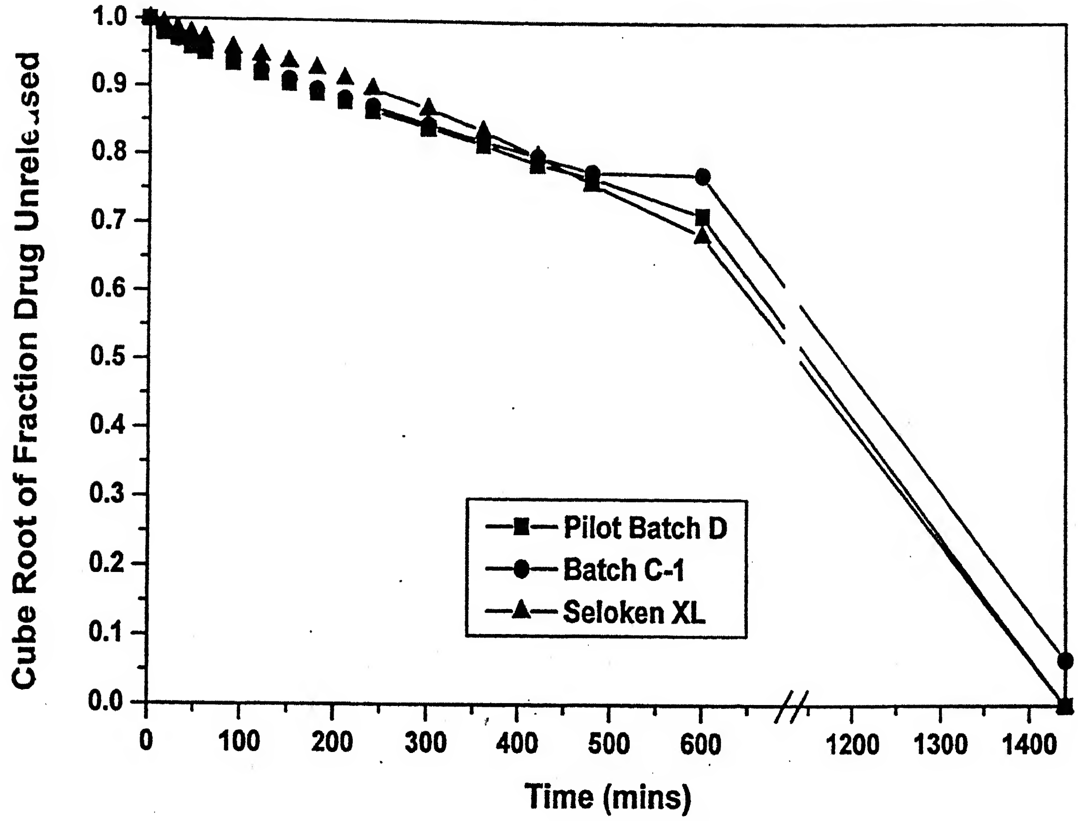


Fig. 8.33. Hixon-Crowell plot.

Table 8.29. Linear regression parameters for Hixon-Crowell model release.

Product	Linear ($y = A + Bx$) Regression Parameter Values				
	A *(intercept)*	*B* *(Slope)*	R (Regression Coefficient)	SD (Standard Deviation)	N (Number of data points)
Pilot Batch D	0.98135 (0.00303)	-0.00046 (0.00001)	-0.99494	0.00744	15
Batch C-1	0.98296 (0.00273)	-0.00045 (0.00001)	-0.99558	0.00671	15
Seloken XL	1.00367 (0.003)	-0.00048 (0.00001)	-0.99526	0.00737	15
Value in the parenthesis is the standard deviation.					

8.9.6. Korsemeyer Model

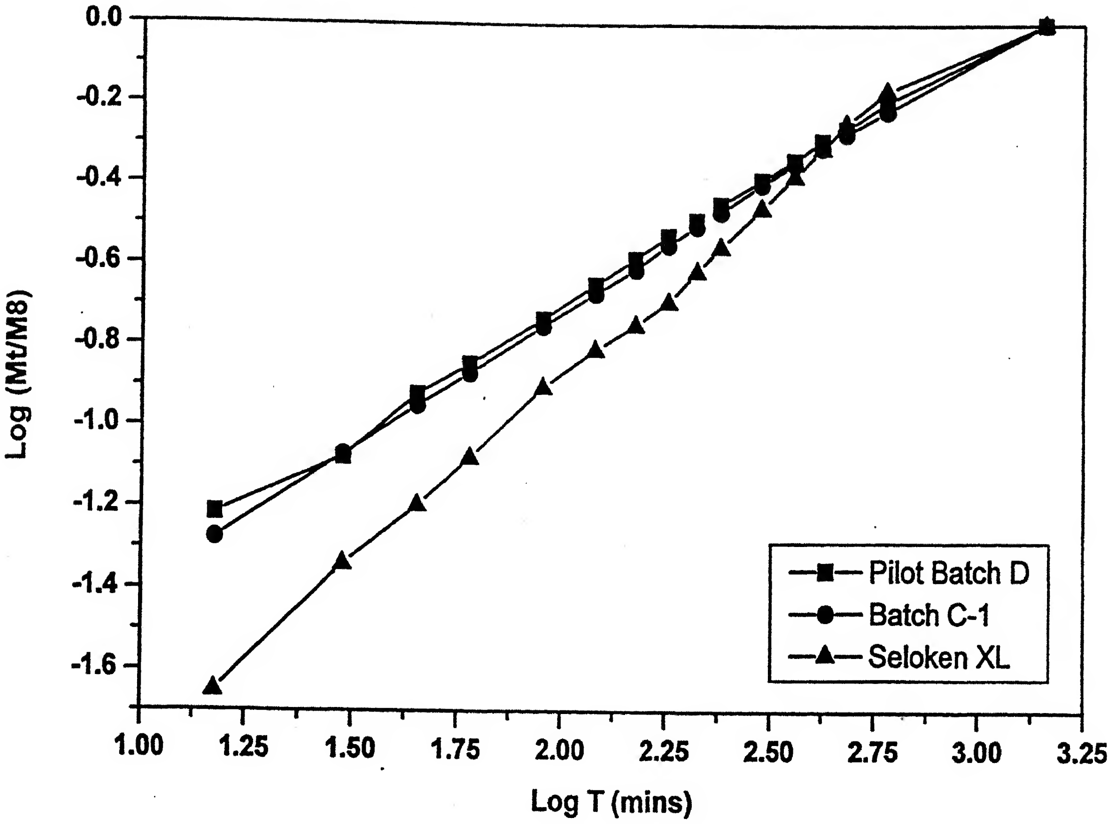


Fig. 8.34. Korsmeyer-Peppas plot.

Table 8.30. Linear regression parameters for Korsmeyer-Peppas model release.

Product	Linear ($y = A + Bx$) Regression Parameter Values				
	A *(intercept)*	*B* *(Slope)*	R (Regression Coefficient)	SD (Standard Deviation)	N (Number of data points)
Pilot Batch D	-198311 (0.01904)	0.63979 (0.00836	0.99881	0.0168	16
Batch C-1	-2.03458 (0.0128)	0.65455 (0.00562)	0.99948	0.0133	16
Seloken XL	-2.63166 (0.04688)	0.87017 (0.02059)	0.9961	0.04136	16
Value in the parenthesis is the standard deviation.					

From the linearity of the curve and the statistical regression values in different release kinetic models, it can be said the release of the drug metoprolol tartrate from the hydrophilic non-disintegrating matrix tablet prepared from the blend of HPMC through a combination of diffusion through the gel matrix and erosion of the matrix[8-12].

8.10. DISSOLUTION PROFILE COMPARISON USING SIMILARITY FACTOR

Comparison between the *in vitro* dissolution data for the RLD Seloken XL 50 and developed batch 'D' established a good similarity between two dissolution profiles with similarity factor f_2 value of 63.8966. The difference factor f_1 value stood at 11.0824[13-17].

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Chapter 9

Summary & Conclusions……

9.1. AN OVERVIEW

Awareness of disease and efforts to gain control over the disease contributed in considerable increase of human life expectancy (25-30 years for the young generation. Life-style drugs improved the quality of life and human performance. All this was possible as the insight to understand diease and its manifestation at cellular and molecular level with advanced technique that were developed in biomedical field and the ability of Pharma-industry to mass produce quality medicines and cheaper prices.

The concept of novel therapeuticals i.e., novel drug delivery systems (NDDS) capable of modifying the rate of drug delivery, altering the duration of action and or targeting the delivery of drug to the tissue are seeking wider acceptance in medical fraternity against the conventional dosage forms that delivers drug which is immediately available for action or absorption without any mechanism being incorporated in the system to have spatial or temporal control over drug release, due to enhanced therapeutic efficacy.

Novel Drug Delivery Systems involves use of new or existing drugs presented in newer forms of delivery. The definition normally includes use of new routes of administration different from the originally accepted ones. The designing and development of such delivery systems involve technological advances. These delivery systems are aimed at altering solubility, improving stability or altering bioavailability. The design and change in process builds in cost of the product. Efforts should be made in reducing the cost of production of NDDS so that the total disease management cost is reduced thereby rendeing economic merit to the patient.

9.2. CHAPTER 1. PHARMATECH INDUSTRY

It takes a review of the constrained pharmaceutical industry in terms of (i) business, product(s) and sale; (ii) survival and growth stratigies, (iii) patent issues – all having implications on their own and to the people. Indian Pharmaceutical Industry is known for its internationally accepted quality products and cost wise the most efficient, in the world. However, Indian share in the global drug industry is very low, less than 2 %. With giant mergers with Indian Pharma Companies, this figure is likely to change under the product patent regime.

Over a year now, there has been lot of apprehensions on the Product Patent which is effective from Jan 2005, as India became signatory to GATT and bound to TRIPS. Opinion expressed by (i) socio-economic experts, (ii) government representatives, and (iii) people have been complied. The 3rd Ammendment Patent Bill was passed in the Parliament on March 22nd,2005. India showed its strength by expressing its will to continue to supply cheaper medicines to industrially underdeveloped countries, especially for AIDS victims. There is a general opinion that these changes in the Bill have been well addressed and protected with end note to 'wait and watch' especially if the cost of the medicine would escalate beyond affordability.

9.3. CHAPTER 2. A SURVEY IN HYPERTENSIVE

9.3.1. Hypertension – Life style disease or ageing symptom

Mental stress – an unwanted supplement gift and blessings of modern life, is being looked as the cause of many diseases. This concept needs to be discriminatively analyzed against the short span of life our ancestors who did not live long due to lack of developed immunity against diseases (vaccines), way of fighting out with infections (antibiotics), unaviability of sophisticated and high-tech medical services (surgeries and transplants), malnourishment, social instability (wars) etc. They did not live long

that the aging symptoms/manifestation of body, especially like hypertension could be clinically detected – in light of limited resources and progress in science. With constant intensive need based research and development in science, technology, and socio-economic policies made medical facilities and medicines available to all. This contributed significantly in the health and well-being of human civilization. However, aging symptoms like hypertension and the complications associated with it (which each one has to live with age) has added another challenge; more so when the patient fails to comply with the drug therapy, as one has to comply for the rest of ones life, once developed (in most or almost all the cases). The two main reasons for non-compliance for drug therapy are (1) cost and (2) drug therapy regime.

9.3.2. Conclusions of Questionnaire Results

A questionnaire study was designed and undertaken in an attempt to study the atttitudial approach to hypertension and non-compliance to drug therapy. The study was performed on a small population in a limited geographical aera (Jhansi), so cannot be a general finding. However, the study results were in line to the reports made by others. Following conclusions could be drawn.

i. Higher ratio of male: female (2.3: 1) undergoing medical check-up.

ii. Majority (~63%) of patients reacted in dismay for they being hypertensive.

iii. Salt and Smoking Control: Amongst the hypertensive, ~82% females and ~77% males were controlling their salt intake. ~24% of men who were smoking and drinking kept a check on their habit.

iv. Nature of Diet and Physical Activity: ~61% females were vegetarian, ~41% of the total study group indulged in walking.

v. Compliance to drug therapy: It was poor. Only ~40% male and ~26% females were regularly taking their medication. The major reason for

non-compliance was their perception to disease and cost. ~57% simply discontinued their medication, randomly, on and off while ~31% due to frequency of dosing who felt it ideal if were prescribed once per day.

vi Side effects: Headache was the most common complaint followed by dizziness.

vii Overweight: Only ~6% were overweight.

9.3.3. Some Interesting findings

- Aawareness to hypertension was higher in females (2.3 times) when the literacy rate in men is higher than women.
- Women folk showed better compliance to (i) drug therapy and (ii) non-medicinal means of controlling the BP – in terms of salt intake, diet etc.
- In general, patients' complaint of headache with medication.

9.4. CHAPTER 3.MARKETED METOPROLOL TABLET EVALUATION

9.4.1. Inspiration and Study Relevance

The results of the survey prompted to evaluate metoprolol tartrate tablets available in market in terms of quality and cost. As the generic products are expected to qualify the Tests, so were our results as anticipated. However, the cost factors worked out for different brand showed considerable difference.

The Indian government has initiated its moves to appeal medical community to practice prescribing active drug rather go brands names, so that the patient is at discretion to opt for cheaper bio-equivalents i.e., generic version. However, until the population is educated for this, the process would simply shift from Doctors's table to Pharmacist's counter. Government's thought of opening "Government Pharmacy

Outlets" for essential drugs to make medicines available at controlled prices in line with the "Government Ration Shops" is a better option to initiate with.

9.4.2. Study Result Conclusions

9.4.2.i. Official and unofficial evaluation

All the tablets under study where within the limits of official specifications in terms of (i) weight variation, (ii) content uniformity, (iii) disintegration test and (iv) drug dissolution. Besides, the requisite tablet organoleptic properties were satisfactory. Therefore, form the from the performed laboratory test data, it can be concluded that all the products were therapeutically bioequivalent. However, tablet coded IR-D had little higher range in which these values fluctuated widely as compared to other tablets.

9.4.2.ii. Comparative Cost Therapy

There is considerable cost variation (~44%) between the tablets. So, prescription of cheaper brand could be taken advantage for and in the interested of patient.

9.5. CHAPTER 4. INTRODUCTION

The present research work deals with the general aspects of New Drug Delivery System. An important avenue of Oral NDDS is its application as "Extended Drug Delivery System" which enables dosing of drug in a sustained or controlled manner so as to provide greater patient acceptance and improved efficacy over conventional therapy. The factors influencing the performance of ER DDS have been reviewed in light of technological and economic feasibility in "ER matrix tablet". ER product evaluations for drug availability including *in vitro* measurements, stability requirements and Regulatory considerations have been mentioned followed by the Scale-Up and Post Approval Changes (SUPAC).

Thus, there is a need to design and evaluate controlled release dosage forms on scientific basis in form of tablets. Against this background, it was considered of interest to design and develop solid oral extended release drug delivery system of antihypertensive drug metoprolol tartrate. The objective also included undertaking *in vitro* evaluation. The objective of the work also kept in mind the possibility of scaling up.

9.6. CHAPTER 5. LITERATURE SURVEY

In order to develop a robust formulation on scientific basis, help was taken of the work done earlier on these as given in the published data. Hydrophilic matrix controlled release systems (along with their advantages and limitations) and the selection of suitable polymer such as HPMC are discussed.

The chapter also deals with the literature reports on the drug molecule employed in this research work. The literature covers the general profiles of these drugs including their description, solubility, therapeutic category, toxicity, storage conditions, handiling, precautions etc.

Apart from the above details, literature on pharmacokinetic and pharmcodynamic parameters, their stability, and dosage forms available in the market or mentioned in the literature are also reported. Analytical methods like spectroscopic, chromatographic that can be used for evaluation and characterization of drugs in solid state as well as in solution form have been described with suitable references.

9.7. CHAPTER 6. INTRODUCTION TO EXPERIMENTAL WORK

This chapter reports different methods published in the literature that form basis for the experimental work done in this study. The chapter includes method for calculation of the dose using different models; describes possible oral extended release systems, importance of preformulation studies, including physical, chemical and spectral methods for their identification.

The chapter also describes in details the Extended Release Tablet Dosage Form with emphasis on technique for manufacturing, steps involved, and different types of processes yielding product. Optimization of the process, evaluation of the dosage form, with emphasis on *in vitro* dissolution methods followed by scale up considerations are also discussed.

9.8. CHAPTER 7. MATERIALS AND METHOD

From here on, the experimental work and discussion goes on. Preformulation Studies were undertaken for physcicochemical characterization of the drug with polymer and excipients to estabilish compatibility before taking up formulation studies.

The method of validation of analytical methods used and the official and unofficial method of evaluation used in the study of developed ER tablet of metoprolol are also dealt. The mathematical treatments used for the obtained data to arrive and meaningful conclusions are also described.

9.9. CHAPTER 8. RESULTS AND DISCUSSION

9.9.1. Physicochemical Characterization of Materials

From the literature provided with the materials and the tests performed; the drug Metoprolol Tartrate (Table 8.1); polymers - HPMC K4M and K100M (Table 7.2);

excipients - Lactose Monohydrate (Section 7.A.3) and Magnesium Stearate (Section (7.A.4) were quality raw material or of official specifications for purity and limit of impurities (Table 7.2 and 8.1); were suitable for use in fabrication of ER DDS of Metoprolol Tartrate.

9.9.2. Drug-Excipient Compatibility Studies

9.9.2.i. Fourier Transform Infra Red Spectroscopy

The overlay curves of pure drug metoprolol tartrate (curve A) with polymer and excipients exhibiting characteristic identical peak absorption at same wave number (fig. 8.12, 8.13, 8.14 and 8.15) indicate the absence of chemical interactions between the active drug and the selected polymer, excipients.

9.9.2.ii. Chromatography

The similar identical R_f values for the pure drug metoprolol tartrate (spot A), polymer (spot B & F), and other excipients (spot C, D, G and H) again confirm the absence of chemical interactions between the active drug and the selected polymer, excipients (fig.8.16 and 8.17).

9.9.3. Spectrophotometric Method for Drug Analysis/Estimation

The instrumetal method and validation tests in terms of accuracy (Table 8.7), precision of assay (Table 8.8), ruggedness for *in vitro* dissolution (Table 8.9), specficity (Table 8.10), limit of detection and quantification (fig. 8.20), linearity and range (Table 8.5 and Fig. 8.18), absorption stability (fig. 8.19) at 275 nm (absorption λ_{max}) in pH 6.8 phosphate buffer and indicantive that the spectrophotometric method of selected drug metoprolol tartrate is suitable for method of drug analysis/estimation.

9.9.4. Standard Calibration Curve and Spectral Absorption Stabililty for Metoprolol Tartrate

The Beer's Law was found to obey between ~ 0-280 μgm/mL (Fig. 8.18) and the drug was stable for 3 days/more (fig. 8.19) for UV-spectral analysis in pH 6.8 phosphate buffer.

9.9.5. Dosage Design and Preformulation Studies

The powder and granule properties of drug and polymer were characterized for it has tremendous influence on tablet and tabelling properties. The physico-chemical properties of the drug were studied (Table 8.1). Though the drug has got inherent properties for tabletting, the flow properties were poor (angle of repose $45^{o}23'$). The particle size distribution of control release polymers was determined by sieve analysis (fig. 8.1 and 8.2), 90% of the polymer size was below 150 μm.

9.9.6. Method of fabrication, formulation variables in the design of ER DDS of Metoprolol Tartrate

Based on the results of performulation studies, the formulation work was initiated and is covered in sections 7.B.4 with the justification. Wet granulation technique followed by direct compression method was used (fig. 7.1). Initially, 11 formulations were prepared at fixed concentration of drug and varying concentrations of controlled release polymer and its blend (Table 7.3 and fig. 7.1).

9.9.7. Evaluation of Formulations and Selection of Batch for Scale up

The fabricated matrix systems were evaluated for its organanoleptic properties (appearance, color, texture etc.), hardness, friability, weight variation, content uniformity, disintegration (Table 8.11 and 8.12); and also in vitro dissolution for 24 hours (Table 8.13; Fig. 8.20, 8.21 and 8.22) with Reference Listed Drug Seloken XL 50 of AstraZenca.

9.9.7. Pilot Batch and Product Optimization

The justification for selection of pilot batch from the various batches is discussed in Section 7.B.4.2. The Master Formula is given in Table Section 7.B.6. The granules and tablets were evaluated for the (i) moisture on compressibility (Table 8.14); (ii) temperature (Table 8.15); (iii) temperature and moisture (Table 8.17); (iv) effect of lubrication (Table 8.18); (v) significant granule and tablet properties like Tapped density, bulk density, Carr's Index, hausner Ratio, Angle of Repose, Uniformity of drug distribution etc (Table 8.18 and 8.19).

9.9.8. Accelerated Stability Studies

Short term (6 months) accelerated stability study was carried out in PVC-PVDC blister as per the ICH guidelines for Zone IV. The tablets were found to be stable (Table 8.20, 8.21 and fig. 8.25). The tablet showed uniformity in content and dissolution. No change in physical, chemical or dissolution characteristics in tablets on Accelerated were observed for a period of 6 months.

9.9.10. Static Swelling Studies

The static swelling studies were performed at room temperature. Anisotropic swelling of the matrix is observed (Table 8.22; fig. 8.26, 27, 28).

9.9.11. *In Vitro* Release and Mathematical Modelling of Pilot Batch with RLD Seloken-XL

The *in vitro* release data with the mathematically modeling data for pilot batch D, optimizing batch and RLD is given in Table 8.23, 8.24 and 8.25. Mathematical modeling of scaled up formulation revealed that the release of the drug from the tablet followed 1^{st} Order Fickian kinetics as computed by Korsmeyer-Peppas equation and Higuchi's equation. The release mechanism is by the combination mechanism of swelling and diffusion.

9.9.12. *In vitro* Dissolution Profile Comparison

The mathematical fit factor has been calculated in this work using the dissolution data obtained for the Pilot Batch and the RLD Seloken XL 50. The value of f_2 found was 63.8966 indicated thereby that the profiles are equivalent.

Based on the f2 factor, it clearly indicated that the preparation developed in the laboratory was similar to the reference ER preparation.

9.10. CONCLUSIONS

The study commenced with the objective to

(1) Understand PharmTech Industry;

(2) Undertake a survey in hypertensive patients to study their attitude for one's own aging symptoms; and non-complicance to pharmacological and non-pharmacological means of controlling the high blood pressure;

(3) Evaluate 50 IR generic forms of marketed product and compare the cost factor incurred in the drug therapy; and

(4) Develop and evaluate extended release formulations of metoprolol tartrarte using hydrophilic polymers, optimize the formulation and process variable, scale up desired batch and study tablet and tabletting properties with respect to ANDA and SUPAC.

The work reported here clearly indicates the stepwise approach of the set objective. The results indicated the objective of the work undertaken has been completely achieved.

Annexure.....

PAPERS
(Research Publications & Presentations)

1. Publications

- A Review on Sustained Release of Cardiovascular Drugs Through Hydroxypropyl Methylcellulose and Sodium Carboxymethylcellulose Polymer, Designed Monomers and Polymers, 1(4) 347-372, 1998.

- Bio-polymer albumin – for diagnosis and in drug delivery, Drug Development and Research; 58(3), 219-247, 2003. Print ISSN: 0272-4391.

2. Papers Communicated

- 3-Month Survey Study of Hypertensive Patients Study in Jhansi City, Journal of Public Health, an international journal.

- Controlled Drug Delivery of metoprolol tartrate from hydrophilic ER HPMC monolithic matrix, AAPS, an international journal.

- Dosage form evaluation and cost valuation in generic Metoprolol IR tablets Generic, Int. J. Pharm., an international journal.

3. Presentations

- Poster
  Pharmacopoeial evaluation of Generic Metoprolol Tartrate Tablets, available in India, International Conference, Chemistry Biology Interface: Synergistic New rontiers, New Delhi, India (21st – 26th Nov. 2004).

- Poster
  A survey study of 250 hypertensive patients in Jhansi (UP), InternationalConference, Chemistry Biology Interface: Synergistic New Frontiers, New Delhi, India (21st – 26th Nov. 2004).

- Poster
  Role of Yoga in Hypertension Management, G. V. Patil, R. Kumar*, National Conference on Recent Advances in Biomedical Techniques, Department of Biochemistry, Bundelkhand University, Jhansi, 284 128, Uttar Pradesh (13th May, 2004)

- Poster
  Drug Release Process From Dissolving Polymers, International Conference on Recent Advances in Biomedical and Therapeutic Sciences, Bundelkhand University, Jhansi – 284 128 (UP) India (13th – 15th Jan., 2004).

- Poster
  Peroral Controlled Release Losartan Potassium For Hypertension, International Conference on Recent Advances in Biomedical and Therapeutic Sciences, Bundelkhand University, Jhansi – 284 128 (UP) India (13th – 15th Jan., 2004).

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